Systemic Arterial Embolism

Pathogenesis and Prophylaxis

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By JOHN MARTIN ASKEY, M D

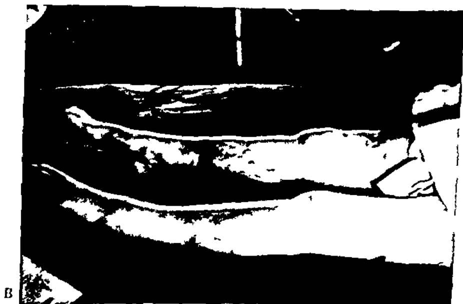
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Fig 1 A Mural thrombi in rheumatic mitral sten[illegible] B Gangrene of the legs following repeated embolism to *bifurcation* of aorta in rheumatic mitral stenosis with gangrene Death from cerebral embolism (By permission of Dr R S Gilfillan and Dr N F Freeman San Francisco)

Contents

the fluids condense and form masses which solidify, it is thus that Nature has sowed in the agents which are the principles of life the secret of our destruction It is particularly in the heart that the fluids coagulate floating polypi may plug the arteries their mass may carry them into various spots and cause various accidents

JEAN BAPTISTE DE SENAC (1749)

Preface

For a clinician to invade so controversial a field of medicine as that of thromboembolism with too definite opinions would seem presumptuous. Many crucial decisions in treatment, however, are based on presumptive evidence which can only be assessed clinically. Periodically he must assemble, analyze, and crystallize the evidence into a workable hypothesis to guide his therapy, even though additional evidence may within the following weeks render certain aspects of his hypothesis obsolete. Many other truths must be learned before we can know, rather than guess, the pathogenesis and proper treatment of systemic arterial embolism. Certain logical deductions, however, can at present be drawn from available evidence.

This book attempts to present the pertinent material which I have derived much pleasure from accumulating and collating. The willingness to help so promptly shown by colleagues was heart warming. My friend for over a quarter of a century, Dr George H Houck, is directly responsible for the book's genesis and was constantly available for help. Many colleagues read certain chapters and contributed constructive criticisms. I am especially grateful to Doctors Myron Prinzmetal, Gurth Carpenter, Howard P Lewis, John I Tragerman, Marcus A Krupp, and C A Peterson.

My associates in practice, Doctors William P Kroger, Clifford B Cherry, Robert C Surridge, A C P Bakos, and Ben Pinsky, gave timely encouragement and suggestions, and my brother, Dr F Vincent A Key, intermittently applied a helpful goad when industry lagged. Dr Charles Dotter and Dr Israel Steinberg were helpful in locating angiocardiographic evidence of left auricular thrombosis, which was courteously supplied by Dr L A Soloff and Dr J Zatuchni. Dr Arthur Bloomfield and Dr Ralph Major read and criticized the historical review.

Permission to use illustrations was generously given by many and is acknowledged in the individual illustrations. Mr Zolton Yuhasz made what I consider beautiful illustrations. The colored photographs were made available by Dr R S Gilfillan and Dr Norman E Freeman. The inclusion of the color plates was made possible by the generosity of my

Introduction

THE PROBLEM

SYSTEMIC ARTERIAL EMBOLISM is a dread complication of any heart disease in which thrombi form in the cardiac cavities of the left side. A high proportion arise from rheumatic heart disease. Such embolism usually is an unsuspected and unpredictable event. The first clinical evidence usually is an occlusion of a large artery. Surgical removal of an occluding clot from the aorta or the arteries of the legs occasionally may be a lifesaving procedure but is not directed at the cause. Furthermore, embolism amenable to surgical treatment constitutes only a small proportion of the total. In the vast majority the occluded artery is inaccessible. This especially applies to embolism of the cerebral arteries.

The number of patients who die or are disabled with the first recognized embolic attack is distressingly high. Many who survive the first recognized episode survive at the cost of an amputated leg if the embolic occlusion is in a peripheral artery, or of a paralyzed side if the occlusion occurs in an artery in the brain. The survivors then face a strong likelihood of further disability or of death from a recurrent embolism. Even the best treatment, if applied after an embolus to an artery is recognized, is often tragically delayed and becomes a treatment of frustration. Satisfactory management must be preventive and deal with the problem much earlier. Effective treatment must be directed either at prevention of formation or of mobilization of the cavitary cardiac thrombi.

In rheumatic heart disease there has been a long preceding period during which the substrate factors which culminate in embolism have been developing. We know little about either the precise pathogenesis of the formation or the mechanism of mobilization of left auricular thrombi. The pathologic stage apparently has been set for years before the appearance of thrombi. The period between the time of formation of a left auricular thrombus and the time of its eventual ejection as a recognized systemic arterial embolus is clinically a latent period.

The time of formation of left ventricular thrombi is not accurately predictable; such thrombi occur in relation to the acute or chronic

friends Mr David Buttolph and Mr Ashton Castle Dr Frederick J Moore helped with evaluation of statistical data

Mrs Margaret Stevenson, with Dr John C Jones permission made essential statistics available My secretaries Grace Munk Hilda Harris and Pauline Conkle and my laboratory technician Esther Amspoker, spent many hours assisting me The help of Leon Lukaszewski of the Audio Digest Foundation was invaluable

For a physician to overlook the many hours of companionship graciously foregone by his wife would be unforgivably remiss I acknowledge her indulgence with gratitude and affection

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The time of formation of left ventricular thrombi is not accurately predictable such thrombi occur in relation to the acute or chronic

endocardial damage of myocardial infarction or congestive heart failure There is no reliable way as yet to tell which individual has a small clot in the heart although angiocardiography promises help in the near future If a thrombus is present no one can predict accurately whether or when it will be dislodged, or if dislodged, where it will occlude an artery A recognized embolic attack, unfortunately, is the first overt clinical evidence of a thrombus in the left cardiac cavities

The chance of a cavitary thrombus being present the likelihood of its mobilization as an embolus, and the risk of death or disability in any individual, at present can only be evaluated statistically Any prophylactic treatment of the individual at present must depend on such statistical data The natural history of systemic arterial embolism must be carefully studied

Evidence has been accumulated to allow an appraisal of the hazard to the individual The unavoidable challenge to the physician is the *need for evaluation of the quantitative risk of systemic arterial embolism* before an occlusion of a larger artery has occurred

The first three chapters will discuss the problem of the risk the morbidity and mortality and the clinical correlations of systemic arterial embolism Chapters 4 5 and 6 discuss the pathogenesis of cardiac mural thrombosis and systemic arterial embolism Chapters 7 8, and 9 consider the diagnostic and prophylactic measures advisable at present in attacking the problem These chapters attempt to blend fact and theory into workable indications for treatment. The evolution of knowledge regarding thromboembolism prior to the present era will be given in the Historical Review

TERMINOLOGY

The term auricle" will refer to the entire inflow cavity from either the greater or lesser circulation The clinician s term body of the auricle and auricular appendage, will be used in preference to the anatomist s terms *atrium and auricle The former terms are well* understood The latter terms we believe are confusing to the American and English clinician By this latter nomenclature the term auricle' *applies only to the auricular appendage* To avoid confusion the term auricle has been abandoned by those using this nomenclature The term atrial appendage has been introduced The consonant terms 'atrial fibrillation and atrial thrombi have been employed instead of *auricular fibrillation and auricular thrombi* The wisdom of such

nomenclature is questioned by many For this monograph therefore we shall use the old terminology

On the other hand the new term antithrombotic will be frequently employed as one at times more precise than the term anticoagulant" Pratt[193] believes that emphasis should be placed on the desirable rather than the undesirable aspects of treatment We believe it meaning is clear and its use acceptable

The study of rheumatic heart disease is essentially a study of rheumatic mitral valvular disease with or without aortic valvular disease Most authors have not included calcified nodular aortic stenosis in their reports although Clawson[44, 4] believes it constitutes 10 per cent of all rheumatic valvular lesions The mitral valve has been involved in well over 90 per cent of the cases reported as rheumatic heart disease

Among the many terms for the surgical correction of deformity of the mitral valve orifice we prefer the term mitral valvoplasty It seems to describe better an operative procedure which must consider not only correcting deformities of the valve leaflet but at times a plastic correction of the papillary muscle and the *chordae tendineae*

Historical Review

ONLY AFTER MANY CENTURIES of observation have we evolved the concept—now so casually accepted—that blood clots form during life in the cavities of the heart and often discharge emboli which occlude the systemic arteries. Indeed, there was a lapse of nearly two thousand years from the first recognition of vascular thrombosis in vivo to the time when it was established that this clotting process could take place within the heart itself. It apparently was Senac [19] who in 1749 first described arterial embolism, but only in the last century has the embolic tendency been clearly traced to its two chief causes: thrombosis in the left auricle due to rheumatic fever and thrombosis *in the left ventricle* due to myocardial infarction.

Hippocrates and his son in law Diocles of Carystus [61] observed coagulation in the blood vessels during life and, as Greeks, they had a word for it—*thrombos*. Galen [8] later agreed that the humor congeal actually in its own surroundings. He Latinized the word to thrombus, but contributed nothing to the concept. His dogmatism so dominated thinking that it was not until the early 16th century that cardiac clot or polyps, as he called them, were described by Benivieni.[1] He and all other physicians considered all clots as having been formed during life, and this misinterpretation led to nearly two centuries of mistakes in cardiac diagnosis.

Kerckering [136] in 1670 first pointed out that cardiac clots actually can form *after* death, but he then fell into completely opposite error and further confused the picture by stating that *all* heart chamber clots were postmortem and utterly insignificant. It was not until 1749 that an unusually brilliant physician thought through the problem. This was Jean Baptiste de Senac,[19] whose concept of thromboembolism anticipated in all essential points the current concept generally credited to Virchow.[53]

As repeatedly happens in medicine his valid concepts, not supported by sufficient evidence, gained no recognition. But regardless of his failure to convince his contemporaries, Senac should be credited with three accomplishments.

First, he clearly differentiated true or antemortem clots or polyps from false or postmortem clots. False polyps, he recognized, are

tho e concretions that form at the end of an illness, or after death true polyps are tho e which have *formed a long time before* the patient dies Fibrous adherent texture he noted was the di tinguishing char acteri tic of true clots they were hard elastic tenacious membranous and yellowish polypoid bodies He added some are o tightly bound to the sub tance of the ventricle that one almost cannot detach them from it.

Senac s second achievement was to describe clearly the three pre requisites for true clot formation—that i , tasis damage to the vessel wall and coagulability Polyps he aid have a predilection for areas where blood flow is arre ted As soon as *movement of the* circulation of the blood is topped the blood *must condense* He thus spoke of the *pause which the blood makes in the heart* When the *blood* does not empty it elf or when the contractions are insen ible or when there is some ob tacle in the pulmonary artery or in the aorta in the auricles or the ventricles *when blood meets barriers* it tends to coagulate Particularly in the *inter tices* of the columns the blood flow is arre ted (all italics mine) The description there fore *clearly applies* to the thrombotic milieu of the left auricle in mitral tenosi

Just as clearly Senac recognized that stasis was *only one of the* necessities to polyp formation which tended *to occur* only where the internal surface becomes *uneven* by some lesion or ome tearing clotting did *not tend* to occur on smooth polished urfaces And finally he recognized that the occurrence and the ize of the clots depended on the coagulability of the *blood* which varied in different conditions. In certain illnes es it is di olved There are other illnesses in which the blood is more di posed to coagulate Thrombosis was initiated he knew in the whi h *matter* of the blood Blood he ays does not coagulate as chee e does that is to say as a uniform matter This lymphatic element was the first to coagulate as a white clot which enme hed the red *cells If* the blood flow was rapid the clots remained white but if the *action* of the blood is feeble he noted the red parts will be *retained in* great quantity and a red clot would form (This is the pre ent concept as to the pathogenesis of white platelet thrombi and red thrombi) Senac described several patients with blood as white as milk and said such blood coagulates ea ily according to various observations

To this clear exposition, Senac added a third achievement He described embolism from cardiac clots to the systemic arteries He described attached clots and those which were 'floating" These floating polyps" he said 'may occupy various places at various times, they may plug the artery in other circumstances the mass may carry itself into various spots and cause various accidents"

Why so little attention was paid to this simple mechanistic theory of thrombosis and embolism is difficult to understand Physicians did not distinguish true from false clots and continued to rely on any clot in the heart as a felicitous explanation for any difficult case Morgagni[170] writing 12 years after Senac's publication, lamented the stultifying effect of the accepted doctrine 'If in the heart of the body after death *have been found a polypus, this was immediately said to have existed* from the beginning of the disorder and to have been the perpetual author of all his evils '

Corvisart,[51] in 1806 even believed that he was the first clearly to differentiate between antemortem and postmortem clots and later on Laennec[147] gave him the credit They either disregarded or were ignorant of Senac s work Senac s mechanistic concept was overshadowed in the first half of the 19th century by the almost universally accepted belief that vascular inflammation with exudation caused all thrombosis and later *by Rokitansky s theory[206] which ascribed all thrombosis to* a crasis or poisoned state' of the blood The theory of humoral pathology says Ackerknecht[2] appeared to contemporaries as ultra modern progressive and scientific

Arrhythmia was early associated with polyps but by a natural error the polyps were considered the cause of any irregularities intermittencies or inequalities of the pulse occurring in their presence This association was emphasized soon after Benivieni first observed clots in the heart Senac (who perhaps is better known because he *reported the value of quinine for rebellious palpitation)* found unevenness of the pulse to be the most reliable sign of cardiac polyps The great Laennec[146] in the historic *De L Auscultation Mediate* supported this causal relation though he made the incredible statement that the polyp could be localized when the pulse was irregular on one side of the heart and regular on *the other Hope[117] in 1842 named among* the general signs of polypi of the heart the pulse is small weak irregular intermittent and unequal It seems highly probable that in most instances these descriptions referred to auricular fibrillation

Thus up to a little over 100 years ago it was accepted that clots could form during life in the cavities of the heart and, characteristically were associated with an irregular action However the *location* of the clots was not correlated with any particular lesion It still was not recognized that most clots in the left auricle occur in mitral valvular disease while those in the left ventricle usually result from endomyocardial necrosis due to coronary occlusion Oddly most reported thrombi were in the right ventricle

Despite the recognition by Senac in 1749 that polyps tend to form in the heart when the blood meets barriers and Vieussens [5] earlier description in 1715 of mitral stenosis with its obvious obstruction to blood flow over a century and a half passed before the high incidence of left auricular clots was generally accepted Osler [1] in his first edition (1893) says It is not uncommon at the examination to find white thrombi in the appendix of the left auricle Occasionally a large part of the auricle is occupied by an antemortem thrombus

The predilection of thrombosis for the patches of roughening on the posterior wall of the auricle was aptly described in 1910 by Sansom [11] who noted their importance as a source of systemic arterial emboli The endocardium lining the auricle is usually thickened in many *cases in patches by chronic endocarditis or atheromatous change The posterior wall of the auricle is most frequently thus affected On the internal surface of this part of the auricle coagula are frequently observed* They may become detached and become emboli which are arrested at some part in the arterial channels A correlation of left auricular thrombosis with mitral stenosis and wall lesions as a source of embolism thus was established by 1910

In 1924 MacCallum [260] emphasized the frequency of these roughened areas and they became known as MacCallum s patches although he did not correlate these patches with thrombosis

All this was progress certainly but while the characteristic lesions associated with left auricular thrombosis were thus being identified the connection between thrombosis and *arrhythmia* was fading into the background In Osler s first edition although the frequency of left auricular thrombi is *emphasized* no correlation with arrhythmia is noted Rapid and irregular action of the heart is correlated only with failure of compensation but not with mitral stenosis and not with clots This omission was not made good even in Osler s eighth edition of 1918 by which time the arrhythmia had been identified as auricular

fibrillation Although clinicians in the 1920s showed increasing awareness of this relationship, it was not until 1930 that Harvey and Levine[111] after studying 111 instances of uninfected mural thrombi (31 with auricular fibrillation), concluded, "there can be no doubt that auricular fibrillation increases the incidence of thrombus formation within the auricles" Other investigators concurred and in 1941, when Hay and Levine[112] analyzed 186 cases to determine the relative importance of age and auricular fibrillation in the development of auricular mural thrombi, they found that fibrillation was the effective factor, regardless of age

The association of mural clots with coronary arterial disease became recognized about 50 years ago, when Huchard[1 1] observed thrombi attached to areas of infarction However, neither he nor anyone else recognized that these thrombi discharged emboli to peripheral arteries He described embolism to the brachial and the left internal carotid arteries without revealing any suspicion as to their origin In their early reports on coronary thrombosis neither Herrick[11] nor Libman[153] mention embolism as a complication One of the first reports on this subject was that of Paullin appearing in 1921[190] Following a severe attack of coronary insufficiency and occlusion the patient's leg became painful then pale and clammy The pulse could not be felt below the popliteal artery At necropsy a mural thrombus was found in the left ventricle and Paullin suggested that "apparently a portion of the thrombus had been dislodged and had plugged the right femoral artery" Since that time arterial embolism in myocardial infarction has become well recognized and greatly feared

1 *Heart Disease as a Cause of Arterial Embolism*

THE FOUR MAIN CAUSES of systemic arterial embolism are rheumatic heart disease, myocardial infarction, chronic arteriosclerotic heart disease, and subacute bacterial endocarditis. The proportion of cases attributed to each cause depends on the accuracy of diagnosis, and many estimates of the causes of embolism were possibly inaccurate in earlier surveys. The differential diagnosis of arteriosclerotic heart disease and rheumatic heart disease in the last decade has been more precise, and the frequency of rheumatic heart disease in middle age and in the aged has been more readily recognized. This may help to explain some discrepancies in estimates.

Among 228 instances of peripheral arterial embolism observed between 1928 and 1947, Haimovici (FIG. 2) found that in 44 (19 per cent) the diagnosis was arteriosclerotic heart disease and in 72 (32 per cent) it was acute myocardial infarction—a total, therefore, of 51 per cent attributed to arteriosclerotic heart disease.[10] In 212 cases of embolic arterial occlusion surveyed by Flasher and Stephenson[7] between 1940 and 1950, 145 (69 per cent) were considered auricular in origin and only 50 (23 per cent) ventricular. Arteriosclerotic heart disease, therefore, was diagnosed only half as frequently as in the earlier survey.

Even before the advent of penicillin therapy, subacute bacterial endocarditis caused only a small proportion of systemic arterial embolism—5 per cent, according to Haimovici's study already cited, and only 3 per cent in Flasher and Stephenson's later cases.[7]

Other causes of arterial embolism are statistically rare. Ventricular mural thrombosis caused by thickening of the endocardium occurs in conditions termed endocardial fibroelastosis or recurrent parietal thromboendocarditis, and can cause arterial embolism. The cause is unknown, with possibly both inflammatory and nutritional factors active.[6] A small proportion of arterial emboli are unassociated with any proven heart disease; they may arise from atheromatous plaques in the aorta, from thrombi in aneurysms, from pulmonary veins, or

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TABLE 1—*Distribution of Thrombi in the Cavities of the Left Side of the Heart in Patients Dying of Rheumatic Heart Disease*

Author	Number of thrombi in left auricle or left ventricle	Number of thrombi in left auricle	Per cent in left auricle
Soder trom	58	56	96 4
Harvey and Levine	9	9	100 0
Garvin	22	20	90 0
Total	89	85	95 3

The danger of systemic arterial embolism arising from cardiac mural thrombi can be measured more accurately than that of pulmonary embolism Whereas pulmonary embolism may arise from thrombi originating in either the peripheral veins or the right auricle, systemic arterial embolism arises in over 90 per cent of cases from thrombi in the left heart In rheumatic heart disease almost all these (TABLE 1) thrombi are in the left auricle (95 per cent of mural thrombi are found there) in nonrheumatic heart disease the majority of thrombi in the left heart are in the left ventricle [3]

DISTRIBUTION OF CARDIAC MURAL CLOTS

It is a reasonable premise that the source of thromboplastin initiating a thrombus is in its immediate neighborhood This source in cavitary thrombosis of the heart is adjacent damaged endothelium The location

TABLE 2—*Distribution of 192 Auricular Thrombi in Nonrheumatic Heart Disease and Rheumatic Heart Disease* *

	Nonrheumatic heart disease	Per cent	Rheumatic heart disease	Per cent
Right auricle	86	65	10	16
Right and left	27	20	17	29
Left auricle	19	15	33	55
Total	132		60	

* From Soderstrom

from the rare phenomenon of paradoxical embolism, in which emboli pass through a patent foramen ovale or interventricular septum The infrequency of these causes is indicated by the fact that Haimovic found no mention of them in his 228 cases Wright Urdaneta and Wright,[77] in studying 107 cases of abdominal aortic aneurysm mention no embolic complications

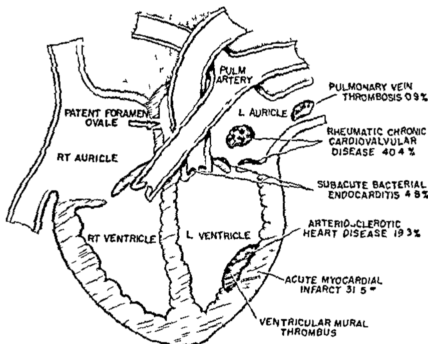


FIG 2 Origin of emboli 228 unselected cases of embolism of the extremities (3 1 per cent undetermined) By permission from Haimovici H Peripheral arterial emboli Angiology (February 1950)

Paradoxic or 'crossed embolism may be suspected if arterial embolism occurs in the absence of obvious cardiac disease and there has been thrombophlebitis and repeated pulmonary infarction [143] The diagnosis is made more often at necropsy than during life

Tumor embolism is usually a diagnosis made by microscopic examination but massive tumor emboli have been described in the brain the spleen the kidney the lungs the liver and the extremities [31] Clots in the pulmonary veins may rarely cause arterial embolism

necropsy however, among 160 cases of either recent or remote myocardial infarction 73 (45 per cent) had a total of 111 peripheral infarcts

The distribution of systemic arterial embolism was studied by Daley and associates[54] in a large series of cases of rheumatic heart disease—TABLE 3 and FIGURE 3 Their estimate reflects experience in practice and

TABLE 3—*Distribution of Arterial Systemic Embolism in Rheumatic Heart Disease Based on Clinical Diagnoses* *

Site of lodgment of 393 emboli occurring in 193 patients			
Site	Number	Total	Per cent
Arteries to the brain		188	47 8
Cerebral	182		
Carotid	2		
Basilar	1		
Retinal	3		
Arteries to the abdominal viscera		56	14 2
Mesenteric	11		
Splenic	17		
Renal	28		
Aortic bifurcation		23	5 9
Iliac arteries		21	5 3
Arteries to the lower extremities		66	16 8
Femoral	29		
Popliteal	21		
Tibial	16		
Arteries to the upper extremities		39	10 0
Axillary	3		
Brachial	36		
Total		393	100 0

From Daley R., et al Systemic Arterial Embolism in Rheumatic Heart Disease Am Heart J October 1951 by permission

probably approximates the true distribution The most frequent sites of lodgment they found are the brain the extremities and the abdominal viscera (kidneys spleen and intestines) Olesen[179] found a similar distribution among 123 emboli in 75 rheumatic patients Jordan Miller Edwards and Parker[13] studied 372 patients with acute and healed

of these potential sites for thrombi determines the distribution in various heart diseases wall lesions in nonrheumatic heart disease are predominantly in the left ventricle and right auricle, in rheumatic heart disease, in the left auricle The presence of stasis in these areas encourages thrombosis The segregation of clots of nonrheumatic origin in the right auricle and left ventricle is quite definite Among 192 instances of auricular clots studied by Soderstrom (TABLE 2) - [3] in 82 the underlying lesion was of a coronary ' type Seventy nine of the 82 were in the right auricle Among 26 instances of auricular thrombi with underlying lesion was of a coronary' type Seventy nine of the 82 were in auricular clots were found in gross nonrheumatic heart disease, the underlying lesions were predominantly rheumatic Myocardial infarction is the chief cause of thrombus formation in the ventricles and its predominance in the left ventricle accounts for most left ventricular thrombi Over 90 per cent of all systemic arterial embolism arises in clots associated with either rheumatic heart disease or coronary arterial disease with or without hypertension Left auricular thrombi of rheumatic origin are presumed to be the cause of most recognized peripheral arterial emboli Left ventricular thrombi account for most of the remainder The incidence of left auricular thrombi in rheumatic heart disease and of left ventricular thrombi in myocardial infarction varies with many factors and will be discussed later

INCIDENCE AND DISTRIBUTION OF EMBOLISM

The actual incidence of systemic arterial embolism in heart disease is not accurately known Clinically detectable emboli represent only the major arterial occlusions and the necropsy examinations are unfortunately numerically inadequate and necessarily often incomplete This is true whether the source be from rheumatic or arteriosclerotic heart.

There is a discrepancy between clinical and pathologic diagnose and between suspected and actual emboli m Warren and Linton [60] found at necropsy an incidence of emboli to the brain spleen and kidney considerably higher than that derived from the clinical study Other studies confirm this Based solely on clinical findings Ole en [1 1] diagnosed systemic arterial emboli m in 75 patients among 351 with mitral stenosis (28 per cent) but found many unsuspected emboli (mostly splenic and renal) at necropsy Hellerstein and Martin [144] found 185 instances of clinically detected peripheral arterial occlusion in 1605 compiled cases of myocardial infarction (11 5 per cent) At

myocardial infarction at necropsy and found the brain and kidneys most frequently involved by embolism

Neither clinical nor necropsy diagnoses give accurate statistical results however because many emboli remain unrecognized Occlusions of smaller arteries often are not even suspected, although they may cause many vague signs and symptoms The mimicry of neurologic disorders in the legs by arterial occlusions has been reported by Gilfillan Jones Rolland and Wylie[90] Many episodes of transitory faintness and dizziness or weakness numbness and tingling of the extremities represent minor cerebral embolism Only a small proportion of the emboli in visceral arteries are recognized even major emboli in the kidney are unsuspected unless they cause pain and hematuria and renal failure may be the result of renal infarction Hoxie and Coggin[120] found that renal infarction from various sources was recognized before death in only two of 205 cases, and Miller Burchell and Edwards[15] found clinical evidence in only one of 44 instances of arterial embolism of the spleen and kidney associated with acute myocardial infarction Many emboli to the spleen and to the mesenteric vessels cannot be diagnosed from signs and symptoms The diagnostic difficulty in all these instances is equal regardless of the source of embolus

Emboli are more frequently suspected and diagnosed in the extremities than in the viscera because of visible signs and more obvious symptoms Based on the symptoms of sudden pain or sudden numbness and coldness in 330 instances of peripheral arterial embolism studied by Haimovici[10] the diagnosis was suspected in 81 2 per cent Of 300 embolic occlusions 17 (5 7 per cent) gave no clinical manifestation Warren and Linton[6] reported sudden onset in only 69 per cent of 110 instances of embolism in the extremities and severe pain in only 55.8 per cent

Even if all potential sites of arterial embolism were examined at necropsy as they are not—notably the arteries of the brain and of the extremities—the findings would still not accurately reflect the incidence of systemic arterial embolism for arterial occlusions and peripheral infarcts often cannot be differentiated as to their origin either embolic or locally thrombotic Although the brain is supposedly the commonest site of embolism the cases in which it is examined are selected and therefore not typical—only 10 cases in 164 in a series by Weiss and Davis[63] Graham et al[101] reviewed a necropsy study of peripheral infarction in 101 patients dying of rheumatic heart disease

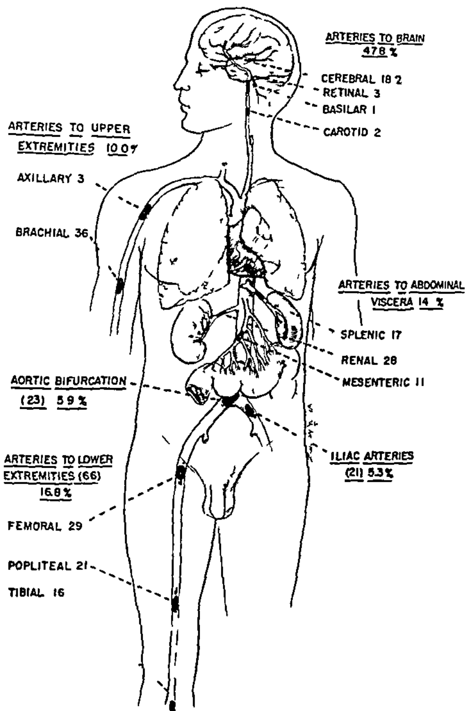


FIG 3 Distribution of systemic arterial embolism in rheumatic heart disease (Figures 3–5 reproduced by permission from Daley R et al Systemic arterial embolism in rheumatic heart disease Am Heart J October 1951)

myocardial infarction at necropsy and found the brain and kidneys most frequently involved by embolism

Neither clinical nor necropsy diagnoses give accurate statistical results however because many emboli remain unrecognized Occlusions of smaller arteries often are not even suspected although they may cause many vague signs and symptoms The mimicry of neurologic disorders in the legs by arterial occlusions has been reported by Gilfillan Jones Rolland and Wylie[99] Many episodes of transitory faintness and dizziness or weakness numbness and tingling of the extremities represent minor cerebral embolism Only a small proportion of the emboli in visceral arteries are recognized even major emboli in the kidneys are unsuspected unless they cause pain and hematuria and renal failure may be the result of renal infarction Hoxie and Coggin[100] found that renal infarction from various sources was recognized before death in only two of 205 cases and Miller Burchell and Edwards[103] found clinical evidence in only one of 44 instances of arterial embolism of the spleen and kidney associated with acute myocardial infarction Many emboli to the spleen and to the mesenteric vessels cannot be diagnosed from signs and symptoms The diagnostic difficulty in all these instances is equal regardless of the source of embolus

Emboli are more frequently suspected and diagnosed in the extremities than in the viscera because of visible signs and more obvious symptoms Based on the symptoms of sudden pain or sudden numbness and coldness in 330 instances of peripheral arterial embolism studied by Haimovici[11] the diagnosis was suspected in 61 2 per cent Of 300 embolic occlusions 17 (5 7 per cent) gave no clinical manifestation Warren and Linton[20] reported sudden onset in only 69 per cent of 110 instances of embolism in the extremities and severe pain in only 55 8 per cent

Even if all potential sites of arterial embolism were examined at necropsy as they are not—notably the arteries of the brain and of the extremities—the findings would still not accurately reflect the incidence of systemic arterial embolism for arterial occlusions and peripheral infarcts often cannot be differentiated as to their origin either embolic or locally thrombotic Although the brain is supposedly the commonest site of embolism the cases in which it is examined are selected and therefore not typical—only 10 cases in 164 in a series by Weiss and Davis[3] Graham et al[101] reviewed a necropsy study of peripheral infarction in 101 patients dying of rheumatic heart disease

but did not mention the number of brains examined and Garvin[84] reported examination of the brain in only 56 per cent of his series

Although the available evidence is incomplete and inaccurate, still it indicates that the brain is the most frequent site of both fatal and nonfatal emboli, and any estimate of incidence based on examination which excludes this site must be considered inaccurate TABLE 4 illustrates how experience of cerebral embolism varies according to specialty The pathologist observes many asymptomatic cases (66 per cent) the

TABLE 4—*Incidence of Cerebral Embolism in Rheumatic Heart Disease*

	Number of systemic arterial embolisms	Number of cerebral embolisms	Per cent	Method of diagnosing cerebral embolism
Graham et al	39	26	66	Necropsy
Weiss and Davis	57	28	49	Clinical and pathologic
Daley et al	393	188	48	Clinical
Bourne	30	22	73	Clinical
Warren Linton and Scannell	337	50	14 6	Clinical

internist only those clinically manifested (48 49 and 73 per cent) and the surgeon predominantly those for whom an operation is being considered (14 6 per cent)

EMBOLIC VERSUS THROMBOTIC OCCLUSION

Unless an artery is seen at necropsy soon after occlusion it is difficult to determine whether the cause was embolism or thrombosis in situ even the microscopic structure between the thrombus and the wall may yield no indication Differentiation must be based therefore on assumption If the evidence is equivocal and if either a thrombus or a significantly roughened area is found on the wall of the heart it is then assumed (not proved) that either a portion or an entire thrombus has been ejected and has caused the occlusion By these criteria most arterial occlusions studied at necropsy after rheumatic heart disease

have been judged embolic Daley et al found thrombi in the left auricle in 25 of 39 patients with clinically diagnosed arterial emboli m and roughening of the wall in 6 others In four of five patients aged over 50 years with the ame diagnosis Glover O Neill Harris and Janton[91] found thrombotic material in the left auricle

Arterial occlusions a ociated with acute or healed myocardial infarction however how by these criteria a much maller proportion of embolic occlu ions. Jordan et al[13] found that in only 29 of 52 instance (55 per cent) of vascular occlusion occurring in 210 patients with acute myocardial infarction was there a corresponding cavitary clot o about half of the vascular occlusions in acute myocardial infarction are presumably embolic The proportion of embolic occlusions was much lower in tho e occlu ions as ociated with healed infarctions In only 8 of 32 instances (25 per cent) of vascular occlusions occurring in 117 patients with healed infarction was there a cavitary clot. Thus only one in four va cular occlusions in healed myocardial infarctions wa presumably embolic It is entirely rea onable that older individuals with arteriosclerotic disease should how a higher proportion of autochthonous than of embolic vascular occlusions In rheumatic heart disea e the average age is lower and there is less peripheral arterial disease It must be remembered however that an occlusion may be of embolic origin even though the pathologi t fails to find a thrombus in the left auricle The entire thrombus may have been extruded as implied by Graham et al[1 1] in reporting the absence of left auricular thrombi in two thirds of a series of peripheral infarcts found in patients with rheumatic heart di ease and as evidenced by case reports of similar findings following arterial occlusions with typical emboli Another po sibility is that auricular thrombi may be mi ed by the pathologist Clots may be di lodged in the course of necropsy Small emboli sufficient to cau e disabling cerebral lesions can arise from small thrombi which lodged between the folds of the trabeculae carneae can ea ily be mis ed Soderstrom calls the clots in the auricular appendage recess thrombi These are often of recent formation and characteristically are attached to the wall by only a tiny stalk or not at all Consequently he comments uch thrombi are easily lo t or di lodged when the l ft auricular appendage is opened at autopsy

Wallach Lukash and Angri t[5] believe that nonbacterial thrombotic emboli may account for a large proportion of emboli m in which there

is no evidence of left auricular thrombi, for in necropsies of 113 patients with rheumatic heart disease and infarctions of the kidney spleen, and brain, they found nonbacterial endocarditis in 28 per cent of those who had left auricular thrombi and in 51 per cent of those who did not They point out that these vegetations may be overlooked as a cause of embolism because they may leave little gross evidence on being dislodged—another possibility which must be considered therefore, in every instance of systemic arterial embolism, even in rheumatic heart disease

Calcific emboli following surgical manipulation of the mitral valve have been reported by various authors [5] Weiss and Davis [63] reasonably maintain that the burden of proof is on those who deny that arterial occlusions in rheumatic heart disease are from left auricular thrombi In the absence of definite localized arteriosclerosis, a peripheral infarct in rheumatic heart disease is more likely to be due to embolic occlusion from a left auricular thrombus than to a thrombus in situ and should be so considered until this source is excluded This assumption would seem to be a wise precaution for avoiding a possible costly error of omission in treatment Immediate surgical intervention is seldom necessary for an arteriosclerotic occlusion but in embolic occlusion of the artery to an extremity it must be undertaken within a few hours A vascular occlusion in the presence of an acute or healed myocardial infarction apparently is about as likely to be due to localized thrombosis as embolism *Temporary observation is justified and a careful* differential diagnosis between embolism and thrombosis must be made

SUMMARY

Systemic arterial embolism arises in over 90 per cent of cases either *from clots in the left auricle of rheumatic origin or clots in the left* ventricle of arteriosclerotic origin Clots in the cardiac chambers are segregated according to the type of disease Whereas arteriosclerotic or coronary *arterial disease causes lesions predominantly in the right* auricle and left ventricle rheumatic heart disease causes lesions predominantly in the left auricle

Rheumatic heart disease *is the most frequent cause of systemic* arterial embolism Because of the urgency of treatment systemic arterial occlusion in rheumatic heart disease should in every instance be considered embolic in origin unless another source *is definitely established*

In arteriosclerotic heart disease however the frequency of thrombotic vascular occlusion makes a more deliberate differential diagnosis advisable Although the incidence and distribution of systemic arterial embolism in heart disease are not accurately known the brain is apparently the most frequent site of both fatal and nonfatal systemic arterial embolism There are several possibilities by which an arterial occlusion may be of embolic origin even though no thrombus can be found in the left auricle

2 Death and Disability from Systemic Arterial Embolism in Heart Disease

MOBILIZATION OF CARDIAC MURAL THROMBI

SINCE THE RISK OF DEATH or disability from systemic arterial emboli in heart disease arises only *after mobilization of cavitary thrombi* the proportion of thrombi liberated is an important datum, but it is unknown. In no series of necropsies following death from heart disease has there been a complete examination of all the possible arterial sites of embolism to correlate with the mural thrombi.

One of the most complete investigations of rheumatic heart disease has been that of Graham et al[101] who examined the brain in most of 101 necropsies. Among 33 patients with thrombi in either the body or the appendage of the left auricle they found clear evidence of systemic embolism in 15 (45 per cent). The studies of these authors and others (TABLE 5) based on the identification of left auricular thrombi either

TABLE 5—*Evidence Regarding Percentage of Left Auricular Thrombi Mobilized in Rheumatic Heart Disease*

	Number of patients with left auricular thrombi	Number with systemic arterial embolism	Per cent mobilized	Method of identifying thrombus	Method of diagnosing systemic arterial embolism
Graham	33	15	45	Necropsy	Necropsy
Jordan et al	42	32	76	Necropsy	Necropsy
Glover et al	130	47	36	At commissurotomy	Clinical
McGoon and Henly	21	11	52	At commissurotomy	Clinical (confirmed at autopsy)
Total	226	105	46		

at operation or at necropsy and on the diagnosis of systemic arterial embolism from either clinical or pathologic findings indicate that in rheumatic heart disease about half of all left auricular thrombi are mobilized The same proportion applies to clots in all cavities of the heart according to other studies[121, 84, 114, 13]

GENERAL DANGER OF DEATH

The danger from systemic arterial embolism in rheumatic heart disease does not usually appear until adulthood but then embolism accounts for a high mortality rate Hebbert and Rankin[115] found that among 45 patients over the age of 50 who died as a result of rheumatic heart disease 16 (35 per cent) died of major embolic incidents Of 121 deaths directly attributed to rheumatic heart disease in patients between the ages of 40 and 80 Wallach et al[6] found 42 (33 per cent) had died of embolism In addition embolism was indirectly responsible for other deaths—in one instance bronchopneumonia had *followed cerebral* embolism Among 68 patients over the age of 40 who died of rheumatic heart disease Soloff and Zatuchni ascribed *the deaths* of 16 (23 per cent) to systemic arterial embolism Selzer[18] found 10 deaths *from* systemic *arterial embolism* among 95 necropsy studies where myocardial infarction was the primary illness Hellerstein and Martin[114] *ascribed* 11 deaths *among* 160 patients with myocardial infarction examined at necropsy as being mainly due to systemic arterial embolism. In another 11 patients arterial embolism was a contributory cause of death

MORTALITY IN SINGLE EPISODES

Bigelow and Greenwood *reported that* of 39 rheumatic patients with systemic arterial embolism seven (18 per cent) died within a *month* after the first embolism but they did *not* state the location of the occlusion Twenty four per cent of 75 rheumatic patients studied by Olesen[109] died *because* of the first *embolic* episode Among 194 patients of Daley et al[4] with clinical *diagnoses* of 395 systemic arterial emboli *widely distributed* the deaths of 23 (11 per cent) were the direct result of a single embolic episode *From* this compiled group of 308 patients with rheumatic heart disease with *arterial* embolism 49 (16 per cent) died as a result of a single episode The immediate mortality *rate* from embolism in myocardial infarction is higher Jordan et al[15] report a 25 per cent death rate in 84 patients with arterial embolism in acute or healed myocardial infarction The mortality *rate* in any study of

systemic arterial embolism depends on the proportion of minor to major emboli recognized, and must be related to the site of emboli in The mortality rate in occlusion of a major artery is high, whereas immediate death does not often follow occlusion of a splenic, renal or brachial artery Embolism to a coronary artery, one of the rarest sites, has perhaps the highest mortality (over 90 per cent) [80]

CEREBRAL EMBOLISM

Embolism to a cerebral artery is the greatest danger from embolism in heart disease, because of its high incidence Next to the rare coronary artery embolism it has the highest mortality rate and not only accounts for the majority of embolic deaths but also causes serious residual effects in half the patients who do not die immediately The risk is indicated by Harris and Levine s [109] report of immediate death in one third of 72 patients with rheumatic heart disease and the death of another 15 per cent *within a period averaging a little over a year* Daley said that half the patients who had one or more cerebral embolisms died from this complication Lenegre Tatibouet and Paris [110] reported the death within a few days of more than a third of 83 patients with hemiplegia in rheumatic heart disease and more or less severe sequels in a third of the survivors Roedenbeck and Bermejo [0] however, reported immediate death of only one of 13 patients with hemiplegia

Among the survivors hemiplegia may be followed by severe persistent motor impairment with partial paralysis Several types of mental disturbance may develop depending on the size and location of the encephalomalacia In 525 consecutive necropsies in a neuropsychiatric institution Towbin [48] found proof of recurrent cerebral embolism as the cause of organic brain disease in 17 patients although this cause had been suspected in only one Five of the 17 patients had rheumatic heart disease—diagnosed before death in only one of them—and two of the five had had recurrent epileptic seizures Another had manic depressive psychosis and of the other two it was only stated that mental changes had been present for many years Besides these five another of the 17 patients had nonbacterial thrombotic endocarditis The other 11 were patients with myocardial infarcts and ventricular mural thrombi

Although improvements in operative technic in mitral valvoplasty have reduced the incidence cerebral embolism still remains one of the most feared complications of mitral valvoplasty [14]

AORTIC EMBOLISM

Embolism to the bifurcation of the abdominal aorta fortunately comprises only about 5 per cent of the total systemic arterial emboli in rheumatic heart disease Death or loss of limb occurs in a high proportion [66, 69]

The mortality with aortic embolectomy is nearly as great as without it.[134, 67] The pessimism of many surgeons is expressed by Taylor [11] Successful aortic embolectomy is so spectacular as to completely overshadow its true medical worth It is fortunate that this procedure does not have to be considered in the light of its general medical benefit Mankind would be far better served if the same time, effort and money would be spent on some dull public health problem It must be noted however that many deaths following embolectomy are due to further embolism and not to the operation which is usually an indicated procedure

ARTERIAL EMBOLISM IN THE EXTREMITIES

Although embolism to the extremities occurs in one fourth of all rheumatic patients with embolism in only one half of these (13 per cent of the total) is it usually dangerous These are the embolic occlusions of the femoral and iliac arteries In embolism of the upper extremities medical treatment usually procures satisfactory recovery but as to embolism of the lower extremities there is a wide variation in reported results as measured by mortality the frequency of gangrene and residual disability There is a good explanation for the variation The danger varies with the location the promptness and aptness of treatment, the condition of the circulation and the likelihood of recurrence of embolism from the original source Impairment of collateral circulation by diffuse arterial damage or stasis due to congestive failure creates a morbid terrain for any arterial obstruction Dye et al [67] attribute the poor results in their series of embolectomies to the precarious cardiac status of the patient.

DEATH AND DISABILITY FOLLOWING EMBOLECTOMY

The high mortality following even good treatment in advanced cases is evident in the 1952 report by Flasher and Stephenson [7] of 212 patients at the Los Angeles County General Hospital. Each of these had

at least one embolic arterial occlusion affecting a lower extremity and 67 per cent died within 30 days of onset Although the patients selected for embolectomy were considered the better risks the mortality among these was slightly higher—70 per cent In general however, the patients were in poor condition when first seen and the authors believed that "the outlook toward life and limb that we have noted certainly will not be as grim in private patients' In contrast Pratt [10] reports two thirds survival in 42 cases of embolism in the femoral artery Medical treatment has improved in the last decade and the results from embolectomy have improved with earlier operation and a better selection of patients In 83 patients without embolectomy for whom the treatment was considered "early and good Silbert [20] records that 71 per cent recovered without gangrene

Earlier embolectomy in a higher proportion of cases was credited with an improvement in limb survival by Warren Linton and Scannell [61] Although there can be little question that the early removal of an embolus to the bifurcation of the aorta or the iliac or femoral artery is advisable still it is advisable only if a trained surgeon anesthetist and internist are available The prevention of the subsequent formation of a thrombus at the site of operation or of the mobilization of another left auricular thrombus is both an immediate and a remote concern

The tragic nature of embolism to the extremities in the past is well illustrated by a case report of over 80 years ago Treatment then was ill advised and futile and the patient usually died after miserable suffering The verbatim report is given here [2]

Embolism of the arteries of the Extremities by Samuel B Ward M D A M—one of the Surgeons to the Presbyterian Hospital New York and Professor of Surgery at the Woman s Medical College of the New York Infirmary The following case appeared in the writer s practice last summer *and the rarity of such together with the poverty of the literature of our own language on the subject* are his reasons for offering this paper for publication

Case 1 *Heart disease of Sixteen Years Standing Sudden Occlusion of Right Popliteal Artery after an Attack of Endocarditis Apparent Improvement and Attempt at Collateral Circulation for Two Days Secondary Thrombosis of Femoral Artery extending as high up as Poupart s Ligament at least and occluding all the Collateral Branches Gangrene of Leg on Fourth Day Double Diaphragmatic Pleurisy and Trismus on Eleventh Day Death on Twelfth*

D P aged 32 Irish married plasterer by trade has never had rheumatism When 16 years old he was told by his physician that he had

heart disea e the character of which was not stated and was advi ed to give up hard work and avoid excitement

August 6 1873—Was first called to ee this patient and found his stomach largely distended with ga bowels omewhat tympanitic pul e 150 irregular and intermittent (mesenteric emboli m? auricular fibrillation?) (Questions and parenthe es pre ent author s)

7th Morning Examination of heart revealed hypertrophy of left ventricle with dilatation and some valvular disea e of the exact nature of which I could not be certain on account of the rapid and irregular action of the organ

8th.—Extreme suffering from dyspnoea during pa t night no oedema of lower extremities at any time

11th at half pa t one while walking acro s the floor he had experi enced a en e of numbne s in the right leg *remarking that he had no* control over it. This was followed almost immediately by exceedingly acute pain in the muscles of the calf compelling him to lie down Dr Cole at once directed the limb to be *bathed in hot mustard water and vigorously rubbed* (Italics pre ent author s) The mu cles were perfectly flaccid the skin *was white* as marble and apparently as bloodle s and the surface from a hand s breadth above the knee to the extremity of the toes perfectly cold Pulsation could be felt in both tibials of the left limb on the right side no pulsation could be felt below the opening in the adductor magnu for the passage of the fem ral *The patient s general condition was indica tive of acute suffering His head and upper extremities were bathed in* perspiration and he tossed about the *bed incessan ly begging some on to shoot him to put him out of his* pain (Italics are pre ent author s)

The dia no is was made of emboli m of the right popliteal artery by a clot or vegetation from the valves of the heart

On the 23rd day at 2 o clock A M he died perfectly quietly it was impos ible to obtain perm sion to make any po t mortem examinati n whatever—a circum tance much regretted

Ward refers to another patient with emboli m to the popliteal artery who was in perfect agony In addition to yeast poultices externally *the internal treatment was supporting and stimulating* (italics present author s) the patient s daily allowance being four pounds of fresh lean beef made into a trong broth three eggs and a sufficient quantity of milk made into punch *and as s mulants* one *quart bottle of brandy one half pint of sherry and one pint of champagne—the latter to con trol nausea* (Again pre ent author s italics) The patient also fre quently took as much as four ounces of laudanum in the 24 hours to relieve pain The modern dosage of alcohol recommend d for periph eral vasodilatation would appear of relatively homeopathic amounts in

supportive, stimulative, and antinauseating effect Ward found only one recovery in 30 published cases of embolism to the extremities

It may seem gratuitous to recall at length the errors of the past, but even today, with modern methods, the treatment of any single embolic episode is one of frustration inasmuch as only the effect (embolism) rather than the cause (cardiac mural thrombosis) is being treated The most frequent type, cerebral embolism is at present inaccessible to embolectomy, and has a high mortality rate Emboli lodge in accessible site in relatively small proportion, and despite the most skillful medical or surgical treatment results are often unsatisfactory Recovery assures no immunity against an early serious or fatal recurrence How great the danger of recurrence may be, we must consider next

MORTALITY IN SURVIVORS OF ARTERIAL EMBOLISM

Duration of Survival Period after Recognized Embolism

Recovery from the first attack of embolism in no way terminates the danger of future embolism but actually increases it Any optimism generated by the survival of an occasional patient for many years without treatment is dampened by an examination of the usual natural history The subsequent natural history in systemic arterial embolism is that of short survival and a high proportion of deaths are due to recurrence Whether the initial embolus is removed or the condition treated expectantly survival is about equally long

The danger is well illustrated by Strombeck s [40] follow up on the 60 "successful cases' of survival following embolectomy for all causes in a group of 327 treated in Sweden (1912 through 1932) A fourth of the patients were dead within a year of operation half of them in three years and two thirds in five years Hemiplegia caused 12 of the 41 deaths and occurred in 4 of the 19 survivors Strombeck [40] observed that since 'these were heart disease patients who had already been exposed to arterial emboli it seems reasonable to assume that a large number of these hemiplegias and perhaps most of them were due to cerebral emboli

Since the sources of embolism were all types of heart disease these figures reflect a general prognosis as to the length of survival following embolism

RECURRENT EMBOLISM AS CAUSE OF DEATH

In sy temic arterial emboli m occurring onl in patients with rheu matic heart disease recurrence is similarly frequent and urvival al o short. Amo g 39 such patients 32 survived for an average of only three and one half years according to Bigelow and Greenwood who

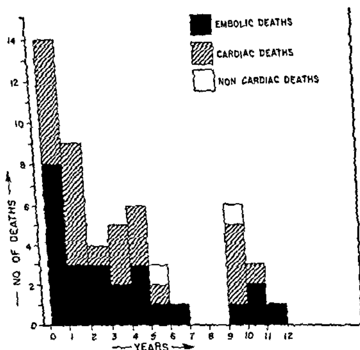


Fig 4 Graph showing fate of 52 urvivors of sy temic arterial emboli m (Type of death)

did not specify the causes of *death* In another group of 52 27 died within 3 years 14 from recurrence[54] (*Fig 4*) Recurrences were early frequent and *serious*

One may approximate the danger of *death* from emt olism in rheu matic heart disea e as *follows* *Of 100 patients* with recognized embo lism about 16 die in the f s a tack and about 38 (45 *per cent*) *of* the surviving 84 die of *recurrent emboli m* Thus the risk of death from embolism in the first or subsequent attacks *is over 50* per cent

The Period of Greatest Risk of Recurrent Embolism

The period of greatest likelihood of recurrent embolism in rheumatic heart disease in the study of Daley et al[54] was immediately after the first recognized episode *In 115 patients who had multiple episodes* about as many had recurrences within a week (32) as did in the next three weeks (41), and as many in the first month (73) as in the next

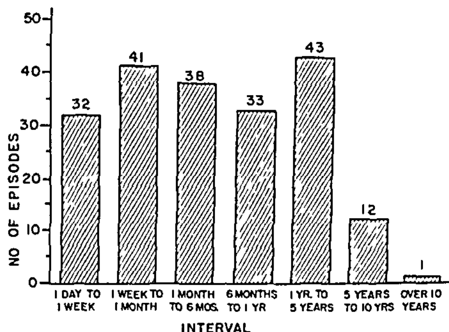


FIG 5 The time interval between recurrent embolic episodes

eleven months (71) see FIGURE 5 Of 201 recurrent episodes within ten years, 144 (or 71 per cent) occurred in the first year The danger continued however not just for a short period after the first embolism but throughout life About half the deaths early or late were due to systemic arterial embolism moreover it could be said of the survivor at almost any time after the initial episode that half of them eventually would die of systemic arterial embolism The danger became progressively less imminent but was ultimately no less certain

The chance of recurrence of systemic arterial embolism in rheumatic *heart disease is thus many times greater than the chance of a primary* episode Once the essential thrombus has formed in the left auricle and

has been mobilized a continuing substrate for recurrent embolism exists Until the underlying mechanism which produced the primary embolism is altered there is no reason to assume recurrent embolism will not be the rule The evidence indicates that once embolism begins it continues In one patient reported by Wright [1] nine emboli occurred within ten days

Although recurrent arterial embolism has not been so well studied in heart disease of nonrheumatic origin and would seem clinically to be less common certain studies indicate frequent embolism arising from ventricular mural thrombi Towbin s [48] report of recurrent cerebral embolism from fragmenting left ventricular thrombi is an excellent clinical prototype Thrombi may persist over a healed myocardial infarct and account for repeated minor unrecognized arterial occlusion

REPEATED EMBOLECTOMY

At times the recurrent emboli lodge repeatedly in sites accessible for removal so that repeated embolectomies are necessary Although the same artery may be occluded recurrences are more frequently at differing sites

Before adequate antithrombotic measures were available to inhibit causative cardiac mural thrombosis recurrent embolism required repeated embolectomy—on occasions a disheartening experience In 1939 Dicumarol was not in use and although heparin was available it was necessary to give it by injection and the need for a prolonged uninterrupted antithrombotic action was not appreciated MacFarlane s case is eloquent.[381]

Case Report An unmarried woman age 27 was admitted to the hospital on April 12 1939 with a diagnosis of acute appendicitis Examination of the heart revealed signs of mitral stenosis with auricular fibrillation and a ventricular rate of 170 Despite the abdominal pain vomiting and tenderness in the right iliac fossa there was no rigidity The leukocyte count was 18,000 It was thought that she might have a small embolic mesenteric occlusion so no operation was performed On April 17 five days later he complained of a numb feeling in the left leg and sharp pain Pallor developed and the pulse could not be felt below the common femoral artery An embolus was found riding on the bifurcation of the common femoral artery and was removed (first embolectomy) Heparin solution was given for eight days and then discontinued The following day April 26 numbness in the right foot developed The foot became cold and cyanosed Pulsation was absent below the right femoral artery A large embolus wa

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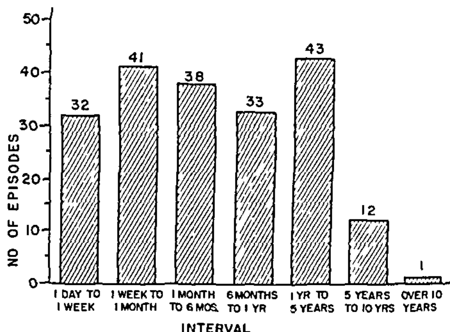


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on [66] obtained a hi tory of previous major embolic epi odes for 6 of 13 patients with aortic embolism

In a study of sy temic arterial embolism in patients with rheumatic heart disea e Daley [54] found that more than two thirds of the survivors of the fir t recognized attack (115 of 171) had at lea t one recurrence—some as many as six—most attacks being within ix months of each other Among Co griff s [5] 35 patients with recurrent emboli m only four had had a single previous epi ode Recurrence is a well e tablished rule, therefore and the pattern of recurrence is as certain from one recognized embolism as from two There is actually greater probability that a patient with one episode will have a second than that a patient with two will have a third

Finally however probable as recurrence may be the seriou ne s of any future episode is unpredictable Any ca e may eventually end like that reported by Teplick and Yarrow [21] whose pat ent with rheumatic mitral valve disea e and auricular fibrillation recovered from emboli m in the renal artery but died uddenly within three months A similar case s described by Linton [2] whose patient recovered from emboli m in an extremity only to die twelve days later from cerebral emboli m The burden of proof would seem to be on those who believe that single epi odes of embolism occur There is little pathologic proof for this belief

In necropsy studies ingle isolated infarcts are the exception the usual finding being multiple infarcts which are frequently of different ages—evidence that they have been ejected not in a single shower but poradically throughout the patient s life [137 17 13]

Among 189 patients studied at necropsy Bull [31] found 301 emboli In the 15 patients with embolism in the extremities there were 30 emboli in other ites besides involving all but one of the fifteen He rather forcefully adjured In g ner [1] it is important not to tare blindly at the extremital embolism, but to remember clearly that the latter is most often noth ng less han a link in a chain of emboli in other organs prior to simultaneous with or sub equent to extremital emboli m The period of potential embolization in rheumatic heart di ease and thus the dange of disability and death is a continuous one from the time of the first emboli m until death Most of the minor embolisms which forewarn of the ub equent major emboli m are clinically unrecognized.

removed and heparin again was given intravenously (second embolectomy) On May 3 seven days later heparin was discontinued The following day May 4 she had sudden lower abdominal pain sacral cramps pain down both thighs and showed some shock No pulsation was felt below the bifurcation of the aorta Doctor MacFarlane said it was with considerable misgiving and a feeling of discouragement that further operative treatment was contemplated A large embolus was found at the bifurcation of the aorta but it was difficult to prevent a portion of the embolus from slipping away The major portion was removed (third embolectomy) Heparin was given continuously again Three days later on May 7 she developed all the signs of another embolus in the right femoral artery! One began to wonder whether the whole thing was futile but after further serious consideration a good sized clot was removed (fourth embolectomy) The clot was located at the right femoral bifurcation Doctor MacFarlane felt that a small piece had escaped into the femoral artery Heparin was continued until May 28 Nine days later on June 6 she had right facial weakness paralysis of the right side of the tongue and a cold blue left arm These findings disappeared however the following day She rapidly regained her strength and was sent home on June 28th

This patient's repeated major arterial embolism (six episodes within two months) which occurred after discontinuance of heparin and required four embolectomies illustrates the danger of rapid recurrence and the necessity of continuous control of coagulability during the period of acute thromboembolism

Gilfillan and Freeman [89] in a personal communication record an early case of a 61 year old woman with rheumatic mitral stenosis and auricular fibrillation Following embolism to the abdominal aortic bifurcation for which embolectomy was done regional heparinization was induced The venous blood in the arms and presumably the blood in the left auricle however was normally coagulable Three days later a second embolism occurred again to the bifurcation of the aorta and embolectomy was again performed The next day death occurred following cerebral embolism At necropsy the left auricle was found to be dilated the mitral orifice admitted only the little finger and an unattached laminated thrombus 2 cm in diameter was found in the left auricular appendage (see frontispiece)

Patients with embolism usually give histories suggestive of previous attacks says Lund [159] In 228 patients with various heart diseases Haimovici found 443 resulting emboli Two embolic episodes per patient was the average reported by Des Prez and Hubay [60] for 28 patients with acute arterial embolism due to rheumatic heart disease Wilkin

3 Clinical Correlations of Cardiac Mural Thrombosis and Systemic Arterial Embolism

Rheumatic Heart Disease

SYSTEMIC ARTERIAL EMBOLISM in rheumatic heart disease occurs in a certain group of patients. Clinicians long have recognized that left auricular thrombosis and systemic arterial embolism are more frequent in those patients with longstanding mitral stenosis, auricular fibrillation and congestive heart failure than in others with rheumatic heart disease without these complications.

The primary correlation of such thromboembolism must be with the formation of left auricular thrombi. In a composite group of 829 patients unclassified as to rhythm or type of valvular lesion studied at necropsy, 216 (26 per cent) had left auricular thrombosis (TABLE 6). This complication can be correlated statistically with both mitral stenosis and auricular fibrillation but, contrary to the general impression, *not* with congestive heart failure, that is, not with clinical failure of the right side of the heart.

Auricular Fibrillation and Right Heart Failure in Rheumatic Mitral Stenosis

The time relation between the onset of auricular fibrillation and the development of right heart failure in mitral stenosis is important

TABLE 6—*Incidence of Thrombi in the Left Auricle (Body or Appendage) In a Composite Group of 829 Patients Dying of Chronic Rheumatic Heart Disease*

Author	Number of patients	Number of left auricular thrombi	Per cent
Soderstrom	219	60	29
Graham et al	101	33	33
Wallach et al	509	123	24
Total	829	216	26

SUMMARY

Probably 25 to 30 per cent of deaths and an inestimable amount of disability in rheumatic heart disease result from the formation and ejection of left auricular thrombi as systemic arterial emboli. In the natural course of this disease process, about one in six of those with embolism die of the first episode, and about half the survivors are dead within three years, nearly half of these because of recurrent embolism. The danger of death in the first attack in rheumatic heart disease is not nearly as great as is the danger of death from recurring embolism.

About 10 per cent of deaths in acute myocardial infarction can be ascribed to systemic arterial embolism. In healed myocardial infarction and arteriosclerotic heart disease with hypertension, the death rate is less. About one fourth die in the first attack. Recurrent embolism as a cause of death in arteriosclerotic heart disease occurs, but it is not as *well documented. Embolectomy, irrespective of the cause of the* embolism, at times is an urgent life saving procedure, but it is applicable to only a small proportion of patients. Next to the coronary arteries (which are rarely involved), the cerebral arteries are the most dangerous sites for embolism. Cerebral embolism is the most frequent, and at present is inaccessible for embolectomy. The survivor of an embolic episode, whether he survives through conservative treatment or through surgical removal of an occluding thrombus, faces the same danger of recurrence. The number of embolisms identified during life is small in comparison to the multiple disseminated embolic infarctions revealed at necropsy.

cally diagnosed s) temic arterial emboli m in rheumatic heart disea-e (TABLE 7) the frequency of this occurrence in those without congestive failure indicates that the thrombi u ually form *before* the on et of congestive failure

TABLE 7—*Congestive Failure in a Composite Group of Patients with Rheumatic Heart Disease and Clinically Recogni ed Systemic Arterial Embolism (Presumptive Evidence of Left Auricular Thrombosis)*

Author	Number with emboli m	Number without congestive failure	Per cent without congestive failure	Comments
Weiss and Davis	26 (Fatal)	17	65	17 had "slight or no evidence of conges tive failure
Bourne	29	24	83	24 had "good exercise tolerance normally ambulatory"
Harris and Levine	72 (Cerebral)	49	68	49 without "rales enlorged liver or edema
Daley et al	194 155 clinical recognition)	125	64	69 had congestive fail ure 41 mild 4 "mod erate "U ual clinical standards"
Ole en	75	49	66	"Right heart failure" in 26
Belcher and Somerville	54	42	78	History of congestive failure in 12"
Total	450	306	68	

Harris and Levine,[104] in a study of 72 cases of cerebral emboli m in mitral tenosis found this complication more likely to occur in tho e with very little objective evidence of congestive failure Bourne[31] reported that of 29 similar instances 24 occurred in patients with good exercise tolerance who were normally ambulatory Facquet Hus on, and Ducrot [0] state that contrary to pulmonary emboli which practically always occur in the bedridden subjects, the peripheral arterial emboli

Auricular fibrillation frequently if not usually, precedes rather than follows right heart failure and in a large proportion right heart failure is a late, not an early subsequent development Olesen[179] studied 206 *patients with mitral stenosis and auricular fibrillation (148 females* and 58 males) for a period of from 3 to 20 years Although 82 (40 per cent) had right heart failure when the arrhythmia was first diagnosed in 73 of these, both right heart failure and auricular fibrillation were present when first seen, and no reliable history either as to priority or to time relationship was obtainable But in the 133 patients in whom the time relation could be determined auricular fibrillation occurred first in 124 and right heart failure first in only nine cases Furthermore in these patients in whom the arrhythmia appeared first there was a long period of auricular fibrillation before right heart failure developed In only 27 of the 124 such patients did right heart failure develop within five years Eighty per cent, therefore went five years without development of right heart failure

Olesen[179] said that the "development of the complete heart failure described from the three stigmata heart size heart rhythm and right heart failure, generally occurs in such a way that the heart first increases in size then auricular fibrillation develops and this is followed at last by right heart failure" Enlargement of the right ventricle occurs after the left auricle has failed The time sequence in the cardiodynamics of mitral stenosis would appear to be first left auricular dilatation and failure eventually auricular fibrillation and last right heart failure

The long survival period of the entire group of 206 patients with auricular fibrillation is instructive Fifty per cent of the females survived six to seven years and 50 per cent of the males survived four to five years This emphasizes the need for a long period of observation in evaluating prognosis as to survival and for the inclusion of the those surviving as well as the deaths The older concept that those with auricular fibrillation died within three and one half years after its recognition is true only in groups observed for a relatively short period of time

Congestive Heart Failure and Left Auricular Thrombi

Diagnosed by the usual criteria—peripheral venous engorgement and edema—congestive heart failure is not present in the majority of living patients presumed to have left auricular thrombi The presumptive diagnosis of left auricular thrombosis is based on an episode of clini

auricular thrombi were present in 44 per cent of patients with pure stenosis in 18.4 per cent of those with predominant stenosis and less than 10 cc regurgitation and in only 9.1 per cent with pure insufficiency—regurgitation exceeding 10 cc

The findings of Janton et al [1 4] in 200 patients were almost identical *Thus a definite correlation of left auricular thrombosis with mitral stenosis is evident* Nearly all patients with left auricular thrombosis have predominating mitral stenosis and 44 per cent of those with pure mitral stenosis have left auricular thrombosis

Auricular Fibrillation and Left Auricular Thrombosis

The correlation between auricular fibrillation and left auricular thrombosis may be studied in a similar way By the incidence of fibrillation in thrombosis diagnosed during life or at necropsy, and conversely by the incidence of thrombi in persons with fibrillation About four

TABLE 8

RELATION OF RHYTHM TO LEFT AURICULAR THROMBOSIS

Percentage of Auricular Fibrillation in Patients with Rheumatic Heart Disease and Clinically Diagnosed Systemic Arterial Embolism (Presumptive Evidence of Left Auricular Thrombosis)

Author	Patients with rheumatic heart disease and systemic arterial occlusion	Patients with auricular fibrillation	Percentage with auricular fibrillation
Ha m [illegible]	92	75	81 5
Harris and Levine	7?	55	76
Daley et al	194	174	89
C k on	69	35	50
[illegible] er and Somerville	54	42	78
Ol en	67	57	85
[illegible] ver et al	84	68	80
Total	632	506	80

strike often the well person carrying on without difficulty in his habitual occupation." They point out that the heart lesion is often so well tolerated that it is the embolism which discloses it. Daley, et al.[illegible] in a study of 194 cases, were unable to correlate the duration and severity of failure with either the onset of systemic arterial embolism or the number of emboli.

It is obvious that one must suspect embolism before the onset of congestive failure.

Mitral Stenosis and Left Auricular Thrombi

The clinician's concept regarding a significant association of left auricular thrombosis with mitral stenosis is readily borne out by studies based both on clinical diagnoses and operative findings. Nearly all left auricular thrombi are found in patients with predominant mitral stenosis and conversely a high proportion of those with mitral stenosis have left auricular thrombi. A correlation based on clinical findings, however, is only presumptive. Clinical diagnoses are not accurate for either left auricular thrombosis or mitral stenosis. Left auricular thrombi can be diagnosed only presumptively if based on the clinical recognition of systemic arterial embolism. The clinical diagnosis of the degree of valvular stenosis and regurgitation is notoriously unreliable. Based on clinical evidence, therefore, one can only state that presumptive thrombosis appears nearly always in patients with presumptive mitral stenosis. In Daley's[24] 194 cases of systemic arterial embolism, mitral regurgitation predominated in only three. The only accurate diagnoses either of left auricular thrombosis or of a valve lesion are those made during life at operation. Only since cardiotomy permitting digital exploration of the left auricle has accurate diagnosis been possible—either of the anatomic type and degree of valvular deformity, or of the functional predominance in flow of stenosis or regurgitation. But more important, for the first time the simultaneous presence of three conditions can accurately be determined and correlated: (1) left auricular thrombosis, (2) the functional valvular lesion, and (3) auricular fibrillation.

Of great value have been the studies of Storer et al.[30] who learned to estimate the degree of regurgitation by immersing a finger in a beaker of water and directing a jet of measured volume against it with a syringe. They classified regurgitation roughly as either more or less than 10 cc. per systole. In 225 cardiotomies it was determined that left

Wherever left auricular thrombi are encountered in rheumatic heart disease therefore—whether during life as diagnosed by clinical arterial embolism during cardiotomy or after death at necropsy—80 per cent are associated with auricular fibrillation Conversely about half of the patients with auricular fibrillation have left auricular thrombosis[24, 232] (TABLE 10)

The chance of a patient with rheumatic heart disease and auricular fibrillation having a left auricular thrombus is about four times that of a patient with normal sinus rhythm

Mitral Stenosis versus Auricular Fibrillation

It is evident that left auricular thrombosis can be correlated with both auricular fibrillation and pure mitral stenosis Forty four per cent of the patients with pure mitral stenosis in 225 cardiotomies had left

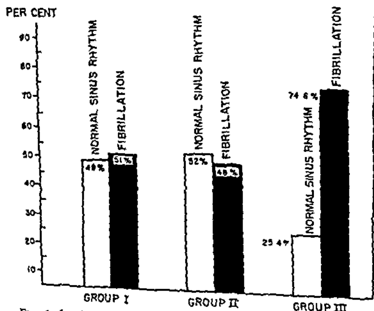


FIG 6 Incidence of auricular fibrillation and normal rhythm in 225 patients who had operation for mitral valvular disease Group I "pure mitral stenosis Group II mitral stenosis plus regurgitation Group III pure mitral insufficiency (Figures 6 and 7 reproduced by permission from Storer J et al Physiopathological concepts of mitral valvular disease J A M A May 8 1954)

TABLE 9—*Percentage of Auricular Fibrillation in Patients Dying of Rheumatic Heart Disease with Left Auricular Thrombi (Necropsy)*

Author	Patients with left auricular thrombi	Number with auricular fibrillation	Percentage
Soderstrom	60	46	76
Jordan et al	50	42	84
Weiss and Davis	25	22	88
Graef et al	14	10	71
Graham et al	33	30	90 9
Total	182	150	82

fifths of those with left auricular thrombi have auricular fibrillation and conversely about half of those with auricular fibrillation have left auricular thrombi Among a total of 440 patients with thrombi found at cardiotomy compiled from five reports the incidence of auricular fibrillation was 86 per cent [14, 131, 1, 91, 70] Auricular fibrillation was also present in approximately the same proportion—80 per cent of 632 cases—of those with presumptive evidence of left auricular thrombosis those in whom systemic arterial embolism was clinically diagnosed (TABLE 8) Further corroboration comes from necropsy (TABLE 9) at which left auricular thrombi were found Again the incidence of auricular fibrillation for this group is 82 per cent

TABLE 10

RELATION OF RHYTHM TO LEFT AURICULAR THROMBOSIS

Incidence of Left Auricular Thrombi at Necropsy in Patients with Rheumatic Heart Disease (Normal Rhythm versus Auricular Fibrillation) *

Rhythm	Number of patients	Number with left auricular thrombi	Percentage
Normal	150	17	11
Auricular fibrillation	170	76	44
Total	320	93	29

* From compiled data of Soderstrom and Graham et al

thrombosis (3 per cent) The addition of auricular fibrillation as a factor cau ed an abrupt rise from 3 to 84 per cent. Thus although about half of all patients with auricular fibrillation without respect to the valve lesion had left auricular thrombi over three fourths of tho e with auricular fibrillation plus pure mitral stenosis had left auricular thromb s is Here the caution of Pearl[291] mu t be remembered Fir t la t and all the time that an ob erved correlation measures nothing and means nothing but a statistical a sociation not causation

Auricular fibrillation appears to have clinical importance chiefly as an index of a composite group of factors strongly predispo ed to throm bc is The correlation between auricular fibrillation and left auricular thrombosis is the mo t accurate we have It is certainly the most helpful to the clinician Of the two correlating factors (auricular fibrillation and mitral stenosis) only the arrhythmia can be diagno ed accurately and identifies the group who have 80 per cent of the sy temic arterial embolism

Estimating Danger of Systemic Arterial Embolism

The danger from systemic arterial embolism for any person can only be e timated ince it is based on the likelihood of three po sibilities first that left auricular thrombi exi t second that they will be mobilized as emboli and third how the lodgment of the embolus will re ult—harmle ly or in paralysis gangrene or sudden death.

The Chance of Left Auricular Thrombosis

In those with no hi tory of systemic arterial emboli m the chance of left auricular thrombosis can be estimated from the rhythm and from the type of *mitral* valvular lesion With *normal* rhythm the chance is about one in ten excluding pure mitral regurgitation With auricular fibrillation however the type of associated *mitral* valvular lesion deter mines the chance of a left auricular thrombus In pure mitral stenosi left auricular thrombosis occurs in about three fourths of those with auricular fibrillation while pure mitral regurgitation reduces the chance in auricular fibrillation to about 10 per cent (FIG 7)

The need for accurate diagnosis of the degree of teno is and regur gitation remains a challenge to the clinician The average clinical diag no tic error in all three groups—pure stenosis pure regurgitation and the mixed condition—is still high but probably will be teadily reduced (TABLE 11) Bjork [3] demonstrated how the left auricle can be cathe

auricular thrombosis, whereas 53.1 per cent of the patients with auricular fibrillation in the same group had left auricular thrombosis

Although pure mitral stenosis identifies the group in which 44 per cent *have left* auricular thrombi, the importance of auricular fibrillation is shown when the incidence of those with arrhythmia is compared

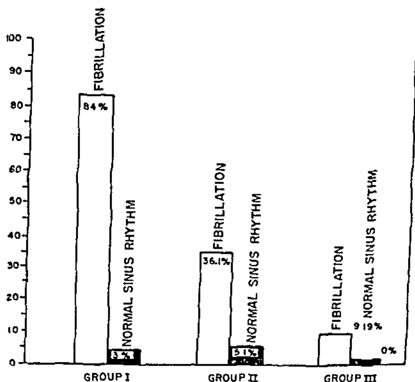


FIG 7 Incidence of left auricular thrombi in those with auricular fibrillation and normal rhythm in the three group Group I pure mitral stenosis Group II mitral stenosis plus regurgitation Group III pure mitral regurgitation

with those of normal rhythm Storer Lisan Delmonico and Bailey [31] reported that among their patients with pure mitral stenosis there were about as many with auricular fibrillation as with normal rhythm—51 to 49 per cent (FIG 6) But among those with fibrillation 84 per cent had left auricular thrombi while among those with normal rhythm there were thrombi in only 3 per cent (FIG 7) Thus although mitral stenosis apparently was essential as a substrate factor for left auricular thrombosis, it was by itself a relatively negligible factor in inducing

without overt embolism and without regard to the type of mitral valvular lesion about 10 per cent (3) in tho e with auricular fibrilla tion and pure mitral teno is nearly 20 per cent and (4) in those surviving clinically recognized embolism regardless of the associated rhythm about 45 per cent. (In tho e with clinically recognized systemic

TABLE 12—*Estimated Chance of Left Auricular Thrombosis Mobili ation of Thrombi and Death From Eventual Embolism in Rheumatic Heart Disease*

Group	100 Patients	Estimated chance of left auricular thrombosis	Estimated chance of mobilization	Estimated percentile chance of death from eventual embolism
1	With normal rhythm (no recognized embolism)	10	5	3
2	With auricular fibril lation (no recognized embolism) with out regard to valve le ion	50	25	11
3	With auricular fibril lation and "pure" mitral stenosis (no recognized embolism)	84	42	19
4	With recognized sys temic arterial embo li m (80 per cent have auricular fibrillation)	100	100	45

arterial emboli m the presence or *imminence of formation of left* auricular thrombi will be postulated Although the individual *percentile* ri k is necessarily approximate the order of arrangement in the order of ri k is logical)

In addition to the ri k of death various disabilities are suffered by a small proportion of the *survivors* *Although* the ri k of embolism may be thus roughly graded and the greater ri k recognized in the patient with pure mitral stenosis and auricular fibrillation the data

terized through a needle introduced into the right paravertebral space and the degree of regurgitation determined He considered this the method of choice Others have used this method and are impressed with its accurate correlation with the findings at operation[133 74 53]

Although the sequelae usually are minor, deaths have occurred following the procedure, in addition to pneumothorax, hemothorax, and cardiac tamponade[30 178 94] Transthoracic catheterization of the left

TABLE 11—*Average Diagnostic Error Made in 225 Patients by Four Groups of Cardiologists* *

Cardiologists	Group 1 (Pure mitral stenosis)	Group 2 (Predominant stenosis minimal insufficiency)	Group 3 (Pure insufficiency)
Group A	25%	34 6%	70%
Group B	27	57 1	27
Group C	35	41 6	63
Group D	24	18 7	100
Average error	*27 75*	*38 0*	*65*

* From Storer et al J A M A *155* 103 1954 by permission

auricle *will* probably *be* used however more and more in *the pre* operative evaluation of rheumatic mitral valvular disease This knowledge will sharpen the accuracy of the prediction of left auricular *thrombosis*

The actual danger of embolism depends of course on the mobilizing tendency of the thrombi This is estimated at 50 per cent for all those with left auricular thrombi (CHAPTER 2 TABLE 5) Although emboli may be minor and unrecognized at first the evidence indicates that if thrombi are being mobilized a recognizable arterial embolism eventually occurs With this occurrence the risk of death and disability from further embolism increases abruptly

By the foregoing criteria i e the rhythm and the type of mitral valvular lesion the approximate statistical risk of death from systemic arterial embolism increases through four groups (TABLE *12*) (1) *in* those with normal rhythm before recognized embolism the risk of death is less than 5 per cent (2) in those with auricular fibrillation

than 40 q cm there were only 52 patients with left ventricular thrombo is (22 per cent) but among the 87 patients with larger infarctions there were 56 (65 per cent)

Thrombosis was more frequent following infarctions of the anterior wall of the left ventricle—in 48 of 115 patients (42 per cent) Among 52 with acute infarctions of the posterior wall there were only 11 instances of ventricular thrombosis (21 per cent)

Congestive failure was mo t frequent in patients who e myocardial infarction was healed but who had ventricular thrombi (70 per cent) it was less frequent in patients with both acute infarction and ventricular thrombi (48 per cent) and lea t frequent in those without ventricular thrombi regardless of the state of infarction Wright Marple and Beck [78] reporting on a study of 1031 cases of myocardial infarction stated that persi tent heart failure predi posed to thromboembolic phenomena and that such failure in a sociation with a large infarct was e pecially favorable to formation of mural thrombi with consequent increa e in the risk of embolism

In e timating the probability of left ventricular thrombo is there fore one mu t determine as far as possible whether there is a myocardial infarction where it is how old it is and how large it is—recognizing that the probability is greater if conge tive failure is also present

One other factor was emphasized by Schlichter Hellerstein and Katz [15] Where myocardial infarction was as ociated with cardiac aneury m they found that 54 per cent of their 102 patients had ventricular mural thrombo is In a control group of 410 patients with myocardial infarction without cardiac aneurysm ventricular mural thrombo is was present in only 21 per cent They did not study the relation of congestive failure but among the 55 with mural thrombi they observed embolic phenomena in 35 (64 per cent)

The important clinical inferences are obvious The danger of sy temic arterial emboli m in rheumatic heart disease is as great before as after th advent of conge tive failure The advent of congestive failure increases predominantly the danger of peripheral venous thrombosis and of pulmonary embolism The important prognostic indexes of potential y temic arterial emboli m are mitral stenosis and auricular fibrillation In arteriosclerotic heart di ease however conge tive heart failure definitely increases the incidence of left ventricular mural thrombosis and con equently the danger of systemic arterial emboli m The pre ence of auricular fibrillation actually has no prognostic value so far as

are useful chiefly as a clinical guide. Embolism occurring in a patient with normal rhythm is just as damaging as that occurring in a patient with auricular fibrillation irrespective of the fact that the original chance of developing it was only one fourth as great. Every patient with rheumatic heart disease must be considered to be in danger of systemic arterial embolism.

Clinical Correlations of Left Ventricular Thrombi

Whereas left auricular thrombosis in rheumatic heart disease is *correlated largely with the presence of auricular fibrillation and the* degree of stenosis of the mitral valve and less with a demonstrable lesion of the auricular wall or congestive heart failure, the formation of thrombi in the left ventricle is largely determined by the character, location and size of the necrotic lesion in the ventricular wall and by the presence of congestive failure. *Nearly all left ventricular thrombi* occur in association with coronary arterial disease or hypertensive cardiovascular disease. Auricular fibrillation is not associated with left ventricular thrombi any more than is normal rhythm. This is illustrated by Jordan's[13] studies. In a series of 327 patients who died either with acute or healed myocardial infarction, 33 per cent had left ventricular thrombi. Twenty seven of the 327 patients had auricular fibrillation but only six of the 27 (22 per cent) had thrombi in the left ventricle. In Garvin's[85] study of cardiac mural thrombi there was no correlation of auricular fibrillation with any cavitary thrombi except those in the left auricle.

The character of the aortic valve apparently has no significant effect *on left ventricular thrombosis. Aortic stenosis associated* with acute myocardial infarction does not significantly increase the incidence of left ventricular thrombi. Kumpfe and Bean[145] found four instances of mural thrombi among 13 patients with aortic stenosis complicating a recent myocardial infarction (30 per cent). This is an average incidence.

Character, Location and Size of the Ventricular Wall Lesion

In a necropsy study of 327 cases of myocardial infarction Jordan et al[13] correlated the incidence of left ventricular thrombi with infarction in several ways. Whereas thrombi were present in 80 of 210 patients with acute infarction (38 per cent), they were found in only 28 of 117 whose infarctions had healed (24 per cent). Another correlation was the size of the lesion. Among the 240 with infarctions no greater

than 40 q cm there were only 52 patients with left ventricular thrombo is (22 per cent), but among the 87 patients with larger infarctions there were 56 (65 per cent)

Thrombosis was more frequent following infarctions of the anterior wall of the left ventricle—in 48 of 115 patients (42 per cent) Among 52 with acute infarctions of the po terior wall there were only 11 instances of ventricular thrombosis (21 per cent)

Congestive failure was mo t frequent in patients who e myocardial infarction was healed but who had ventricular thrombi (70 per cent) it was less frequent in patients with both acute infarction and ventricular thrombi (48 per cent) and lea t frequent in those without ventricular thrombi regardless of the state of infarction Wright, Marple and Beck [6] reporting on a study of 1031 cases of myocardial infarction stated that per i tent heart failure predi po ed to thromboembolic phe nomena and that such failure in as ociation with a large infarct was e pecially favorable to formation of mural thrombi with consequent increase in the ri k of emboli m

In estimating the probability of left ventricular thrombosis there fore one mu t determine as far as pos ible whether there is a myocardial infarction where it is how old it is and how large it is—recognizing that the probability is greater if conge tive failure is al o present

One other factor was emphasized by Schlichter Hellerstein and Katz [1] Where myocardial infarction was a ociated with cardiac aneury m they found that 54 per cent of their 102 patients had ven tricular mural thrombo is In a control group of 410 patients with myo cardial infarction without cardiac aneurysm ventricular mural throm bo is was present in only 21 per cent They did not tudy the relation of conge tive failure but among the 55 with mural thrombi they ob served embolic phenomena in 35 (64 *per cent*)

The important clinical inferences *are* obvious The danger *of* systemic arterial emboli m in rheumatic hea t d sea e is as great before as after the advent of congestive failure The *advent* of congestive failure in creases predominantly the d*anger of peripheral* venous thrombosis and of pulmonary embolism The important *prognostic* indexes of potential sy temic arterial embolism are mitral stenosis and auricular fibrillation In arteriosclerotic heart di ease however congestive heart failure defi nitely increases the incidence of left ventricular mural thrombosis and con equently the danger of *systemic arterial* emboli m The presence of auricular fibrillation actually has no prognostic value so far as

it reflects the presence of more left ventricular mural thrombi than normal rhythm, save that frequently it is associated with congestive failure—a definite thrombotic factor

SUMMARY

1 Left auricular thrombosis and systemic arterial embolism in rheumatic heart disease can be correlated with both mitral stenosis and auricular fibrillation

2 Auricular fibrillation is the most helpful correlate It is easily recognized and identifies 80 per cent of the patients who will have *systemic arterial emboli*

3 Left auricular thrombi in rheumatic heart disease in mo t instances, are unrelated to congestive failure (right heart failure)

4 The risk of death from systemic arterial embolism in any person with rheumatic heart disease depends on the chance of an exi ting left auricular thrombus and the chance of systemic arterial embolism The e chances can be estimated by a composite evaluation of three factor the heart rhythm the type of mitral valvular lesion and the previous occurrence of embolism (TABLE 12)

5 Left ventricular mural thrombosis almost invariably occurs in nonrheumatic heart disease and over 90 per cent of the instances occur in association with coronary arterial disea e or hypertensive cardiovascular disease Left ventricular mural thrombosis can be correlated with the character of the endocardial lesion (its age size and location) Auricular fibrillation cannot be correlated with the formation of clots in the left ventricular chamber in arterio clerotic heart disease Congestive heart failure, of little correlative significance for left auricular mural clots in rheumatic heart disease is definitely correlated with the formation of mural clots in the left ventricle in arteriosclerotic heart disease

4 *Pathogenesis of Vascular Thrombosis*

ALTHOUGH FOUR FIFTHS of the left auricular thrombi in rheumatic heart disease are found in patients with both mitral stenosis and auricular fibrillation the precise pathogenetic connection between these findings is unknown About half of those with rheumatic heart disease and auricular fibrillation have left auricular thrombosis—why we do not know nor do we know why the other half do not form thrombi We know much more about when and where thrombosis occurs than we do about why and how it occurs The precise mechanism of blood clotting even in a test tube where interacting components may be assembled in a fairly constant relationship is not known and the confusion over such a static system is multiplied manifold when one attempts to understand the intravascular clotting of blood in a dynamic system

For a relatively simple clinical concept of thrombosis the underlying factors may be reduced to the historical triad of Senac and Virchow[1-3] the thrombotic stimulus of damaged endothelium the coagulability of the blood and the degree and duration of stagnation in blood flow Regardless of the approach to the problems of thrombosis says Jaques[1] the evidence must clarify the mechanisms by which these three postulated factors operate

THROMBOTIC STIMULUS OF DAMAGED ENDOTHELIUM

Clinical thrombosis occurs at a site of endothelial damage damaged either by inflammation or atherosclerotic degeneration or secondarily as a result of stasis of blood flow[189] In arterial thrombosis endothelial damage is usually obvious and is due either to atherosclerotic roughening or to inflammatory changes In the presence of intimal roughening stasis of blood flow then increases the likelihood of thrombosis Thus thrombosis in the cerebral coronary mesenteric and extremital arteries occurs typically at an atherosclerotic site and more frequently in stasis due to congestive failure Indeed it is rare to find arterial thrombosis without evidence of preceding endothelial damage Occasionally Kars-

ner[133] says the amount of arterial damage 'may be so slight as not to be demonstrable morphologically

The likelihood of thrombosis bears a relation to the type of endothelial lesion Among the diseases involving arteries thrombosis occurs readily in thromboangiitis obliterans and thrombotic thrombocytopenic purpura, less so in the arteritis of systemic lupus erythematosus polyarteritis and scleroderma and only rarely in rheumatic arteritis[13, 234] In atherosclerotic roughening of the intima the tendency varies There is a selectivity of site not always easy to explain Platelet thrombi—the so called aortic oysters'—may adhere to a plaque in the abdominal aorta even though the stream is relatively fast Conversely although Johnson and Baggenstoss[118] found evidence of arteriosclerosis commonly in the mesenteric arteries it was seldom accompanied thereby thrombosis except in cardiac failure

STASIS OF FLOW

The tendency to propagation of a thrombus after it has occluded the lumen of an artery varies with the type of artery and the type of flow The tendency of a coronary artery thrombus to propagate is not as great as in other vessels In a necropsy study of 327 hearts with myocardial infarction Miller Jordan Parker and Edwards[174] found very few thrombi more than a centimeter long Linton[157] however found rapid and extensive distal propagation of an embolus occluding an artery of the extremity involving even the small tributaries of the peripheral arteries and stated 'A thrombus may form distal to an embolus as early as nine hours after the occurrence of the emboli m By then it may be so extensive as to prevent the return of the circulation to the extremity

Venous thrombi arise in many instances where there is stasis without any perceptible underlying endothelial damage—for example in valve pockets of peripheral veins as shown by Paterson and McLachlin[1?] who found no lesions even microscopically As in arterial thrombosis the selection of sites is inexplicable although stasis in certain venous systems increases the likelihood of thrombosis—e g congestive failure in peripheral cerebral and prostatic veins In other systems despite stasis thrombosis occurs rarely In the liver although the central blood flow may be rapid congestive failure causes passive engorgement of the blood in the sinuses and in the mesenteric venous radicles and

increa es portal pre sure nevertheless, intrahepatic thrombo is is rare under the e conditions and mesenteric venous thrombosi in con tradistinction to mesenteric arterial thrombosis cannot be correlated with congestive failure as cited from Johnson and Baggen to [81] In only 9 of 99 cases of mesenteric venous thrombosis collected from the necropsy files of the Mayo Clinic from 1911 to 1915 was cardiac decom pensation con idered a factor In view of the large number of deaths from congestive failure the rarity of thrombo is in the portal sy tem apparently excludes tasis as a significant thrombotic factor in this area Prolonged ta is likewi e has little thrombotic effect in varices of the leg veins in varicocele and in the leg veins of paraplegic patients [49]

Normal blood undoubtedly has all the components nece sary for intra va cular fibrin coagulation but the normal thrombopla tic activity i not ufficiently concentrated to initiate coagulation ince it must interact with the blood for a certain period Alexander [4] believes that clotting occurs continuou ly as a normal physiologic process within the circula tion Thromboplastic activity is the mo t pecific term now pos ible for an intricate and poorly understood mechani m Trauma obviou ly can tear the intima of a ves el and liberate extrava cular tis ue thrombo pla tin into the lumen The mechanism of platelet agglutination fu ion and interaction of a platelet factor with a pla ma factor to initiate thrombopla tic activity is well known The potential sites of thrombo is presumably are those areas where thrombopla tic activity can be gene rated in ufficient concentration—areas of endothelial damage or tasi where there is also sufficient time for interaction of thrombotic com ponents to form fibrin

COAGULABILITY

How does thrombo is occur? A clinician hould probably not attempt to ay much about it Owren [133] states that increa ed coagulability is probably related more clo ely to thrombopla tic activity than to any other component Increased tickiness of platelets increased number of platelets and increased concentration of a conversion accelerating factor have been ugge ted as accounting for the increased incidence of thrombo is in certain pathologic and physiologic conditions [84]

An unfortunate schi m has existed for years between those interested in blood coagulation and tho e intere ted in thrombosis Robb Smith [?]

complains "If one looks in any of the standard works on haematology written during the last sixty years there is scarcely any mention of the mechanism of thrombosis although there will be much discussion of blood coagulation

There is no agreement even regarding clotting in vitro Link[156] regretted "the bloody polemic between experts over the estimation of prothrombin Although the disagreements in the field of blood clotting perhaps are now less sanguinary, the "coagulationists," as he terms them, are still divided The scheme of blood coagulation as worked out up to the present is illustrated well by Alexander[4] The intricate laboratory tests for measuring the various components are available in Tocantins[17] book

Any accurate prediction for thrombosis, then, must be based on knowledge of the relative values of the three factors discussed above The clinician knows which diseases are likely to cause thrombosis and —equally important—he knows the areas in which thrombosis is likely to occur, but as yet he has no reliable way to identify the *patient* in *whom it will occur Blood whether normal or abnormal does not clot* at every area of damage and stasis there seems to be a threshold value that permits thrombosis at one site but not another It is impossible to measure either the individual or the composite values of the thrombotic and antithrombotic factors at a given site, but frequently thrombosis can be correlated with a local predominance of one factor over another In one person the character and extent of the vascular damage may outweigh the factors of blood flow and coagulability although of course it is impossible to measure the character and extent of vascular damage in every site of potential thrombosis In another person stasis may be the precipitating factor but this likewise cannot be measured in a localized area

Laboratory Tests

There remains for consideration the coagulability of the blood All tests for this factor face a common objection The tested blood is a biased sample not a *representative aliquot part of the blood The values* of some thrombotic components prothrombin and its accessory and conversion factors are considered to be the same throughout the blood whether arterial or venous, but the crucial value—the rate of thromboplastic production at the site of endothelial damage—cannot be meas

ured from a sample of peripheral blood To predict thrombosis it would be neces ary to know the inherent thromboplastic potency of the site the time required for this degree of thrombopla tic potency to interact with the availat le prothrombin to form fibrin and whether the rate of flow at that particular point will permit the necessary duration of inter action Prediction te ts determine the clotting time under a number of condition but none of these conditions exi ts in vivo There are many vital di crepancies as well as imilarities *

The existence at times of a hypercoagulable state which initiates clotting at predi posed vascular sites is clinically accepted but not well understood Tests now available more often than not fail to detect any alterations in coagulability Irrespective of the degree of increased coagulability however clotting does not occur on smooth undamaged endothelium in a swiftly moving stream Thrombosis occurs only at certain predi posed sites

Increa ed blood coagulability as a precipitating factor in thrombo is is probably of no greater importance than increa ed values for the other two thrombotic factor Thrombosis occurs frequently with nor mally coagulable blood where the precipitating influence has been an increase in the degree of endothelial damage or an increase in th degree of tasis

With all these factors weighed *it appears that the predisposition of the area to thrombosis is more important than the predisposition of the blood* The probability of thrombosis cannot be predicted by blood te ts so there seems little justification for their routine u e Stati tical data furni h more accurate predictions Farmer and Southwick [71] and others have formulated schemes ba ed on clinical correlations for predicting a patient s tendency to postoperative venous thrombosis

SUMMARY

Potentially thrombosis may occur at any site of either primary in flammation and degeneration of vascular endothelium or secondary changes following stasi Specifically it occurs when the blood flow permits sufficient time for the interaction of thromboplastin and the

* s K el d Lo d Kelvin sa d If you un er tand som thing you can mak a mod l of it and some t me later I think it was J B S Haldane wh id that If you make a mod l of omething you und r tand the mo el "

other thrombotic components Since this interaction time in vivo is virtually impossible to measure in vitro predictions based on clinical statistical evidence are more accurate than those based on any blood tests now available Hypercoagulable blood occurs, but cannot ordinarily be detected An unpredictable increase in any one of the three thrombotic factors—endothelial damage stasis or coagulability—may initiate thrombosis

5 Pathogenesis of Cardiac Mural Thrombosis

LEFT AURICULAR THROMBOSIS IN RHEUMATIC HEART DISEASE

AURICULAR FIBRILLATION in rheumatic heart disease is associated with an increased incidence of left auricular thrombosis irrespective of the type of mitral valve lesion.

The incidence of left auricular thrombosis is slightly higher in pure mitral regurgitation, higher still if stenosis plus regurgitation is present, and very high in pure mitral stenosis.[36] It is not the lesion, however, but auricular fibrillation which is the primary correlate. Nearly all left auricular thrombi occur in predominant mitral stenosis, but the highest correlation occurs in those with pure mitral stenosis who have auricular fibrillation. It follows then that the mechanism of fibrillation must involve an increase of one or more of the three essential factors in thrombosis—auricular endothelial damage, increased coagulability of the blood, and retardation of blood flow in the auricle. What is the difference between patients with auricular fibrillation and those with normal rhythm in regard to these factors, and why is this difference so much greater in pure mitral stenosis?

First, is left auricular endothelial damage more frequent in auricular fibrillation? Pathologists accept the presence both of Aschoff's bodies and of certain other characteristic inflammatory changes as evidence of rheumatic inflammation. There is no evidence that either of these lesions is more frequent in the fibrillating left auricle than in the auricle with normal rhythm.

Aschoff's bodies, indicative though they are of rheumatic inflammation, are actually rarer in patients with thrombi.[69, 9, 6, 49]

The same rarity of Aschoff's bodies is conspicuous in auricular fibrillation.[140, 144] Also, the patients with Aschoff's bodies are younger than those without this finding.[161, 9]

It appears that the acute rheumatic lesion in either the blood vessel or the heart has little thrombotic potentiality. Von Glahn[4] has shown that there is little tendency for thrombosis in acute rheumatic arteritis

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It appears that the acute *rheumatic lesion* [illegible] of the heart has little thrombotic *potential* [illegible] that there is little tendency for thromb[illegible]

was in a 38 year old man with mitral stenosis and regurgitation and auricular fibrillation—its volume was 3200 cc.[39]

In mitral stenosis normal rhythm is associated with an increased ventricular filling gradient manifested during middle and late diastole. Catheter studies of left auricular pressure in mitral stenosis in normal rhythm show a giant "a" wave that presumably reflects an increased auricular systole and presumably accounts for the increased ventricular filling gradient.[178] How much quantitative contraction this graphic record reflects and how much of a factor it is in diminishing it is in the greatly dilated left auricle is speculative. As a matter of fact there is only a slightly increased degree of left auricular dilatation and presumably stasis in auricular fibrillation.

In a study of a group with pure mitral stenosis, Lewis et al[1] found no greater proportion of large left auricles as graded by fluoroscopic examination in those with auricular fibrillation than in those with normal rhythm. There is evidence, however, obtained at cardiotomy and by angiocardiography that auricular dilatation is slightly greater in auricular fibrillation. Wood[79] observed a significant difference at cardiotomy. In 150 cases of mitral stenosis the average enlargement with normal rhythm was 1.45 and with auricular fibrillation 1.76.

Soloff, Zatuchni, Stauffer and Kelly, measuring the volume of the left auricle by angiocardiographic technics, found the normal to be 100 cc. As calculated from their observations, the volume in pure stenosis with normal rhythm was 425 cc; in auricular fibrillation 543 cc. This four- to fivefold increase would be reflected in a greater residual volume and consequently greater stasis, particularly in auricular fibrillation; nevertheless the increase in *degree* of stasis would hardly seem to be as important as the long *duration* of stasis which fibrillation signifies. The patients with auricular fibrillation had an average age of 44; those with normal rhythm 34.

Significance of Auricular Fibrillation

The chief clinical features in auricular fibrillation are the greater age of the patient and therefore, in most cases, the greater duration of the disease. The average age, according to Lewis et al,[1] is seven years greater in fibrillation. DeGraff and Lingg[8] found the average duration of life after the onset of rheumatic heart disease was 18 years for patients with fibrillation as against 15 for those with normal rhythm. The greater age at death of patients with auricular fibrillation indicate

that the arrhythmia develops later in the cour e of rheumatic heart di ea e

As I cnzmetal et al[138] tate it i not auricular fibrillation but the concurrent tagnation that tends toward thrombo i The importance of fibrillation i in identifying a prolonged duration of rheumatic heart di ea-e It occur as frequently in mitral teno is with regurgita tion a in pure mitral steno is and even more frequently in pure regurgi

TABLE 13—*Relation of Varying Thrombotic Factors in Rheumatic Mitral Disease to Left Auricular Thrombosis*

Le i n	Degree f endothelial lamage	Coagulability of blood	Durati n of ta i Short	Prolonge l	Incidence cf left auricular thrombi
Mitral regur itation N rmal rhythm	+	+	0	0	Minimal
Mitral ten i N rmal rhythm	+	+	+	0	10
Mitral steno is Auri ular fil rillati n	+ (l m er ta i)	+ + (older a_e)	0	+	40

tati n [3] Coincidentally it marks a prolonged duratic n of any of the e conditions Thu it identifies pure mitral teno is as prolonged left auricular tagnation tenosis with minimal regurgitation as prolonged but moderate stagnation and pure regurgitation as prolonged but minimal tagnation It affects per e the actual mechani m of throm b i only lightly but does in particular mark tho e patients with the greate t likelihood of thrombo i

At the time auricular fibrillation appears in mitral tenosis n t only i tasis prolonged but the patient is older (coagulability greater) and the endothelium has been sul jected to the damaging effect of pro longed ta i All three thrombotic factors are coincidentally at the maximum The correlation between auricular thrombi and auricula fil rillation therefore predominantly measures a stati tical rather than

a causative association The arrhythmia contributes little to the three thrombotic factors—stasis, coagulability, or endothelial damage—but it accurately indicates that these factors *are at a maximum* (TABLE 13) Prolonged rheumatic heart disease frequently gives rise to auricular fibrillation and prolonged left auricular stasis frequently gives rise to left auricular thrombosis *When these two causative conditions occur* together a high proportion of the patients have both auricular fibrillation and left auricular thrombosis two independent effects arising together *from a common origin but associated so frequently that auricular* fibrillation is an important index of left auricular thrombosis in the patient with pure mitral stenosis

LEFT VENTRICULAR (MURAL) THROMBOSIS

In myocardial infarction, only one of the three thrombotic factors *is presumably the same as in rheumatic heart disease—the coagulability* of the blood which as in rheumatic heart disease probably varies only according to the patient's age The second factor the thrombotic *tendency of the damaged endothelium* is much higher in *myocardial* infarction The readiness with which thrombosis occurs can be better appreciated when it is remembered that although the ventricle is actively contracting *and the aortic valve operating freely* the clot *forms within* a few days after arterial occlusion, and at times even when prothrombin activity has been reduced to 30 per cent of normal Although the ven*tricular wall does* not contract *strongly* in the immediate area *of the* infarction this localized inactivity with the remaining heart muscle actively contracting should have only a minor effect on the movement of blood over *that* area

If this strong thrombotic tendency can exist without significant stasis it should be greatly enhanced when stasis is obvious Congestive heart *failure which is usually associated with left ventricular enlargement* increased residual volume and resulting stasis is found in twice as many cases of myocardial infarction with as without ventricular clots *The higher incidence of mural thrombi in infarcts of the anterior wall* is attributed by Jordan et al[14] to the probably greater stasis at the apex in the presence of a large infarct especially in congestive failure

Since this process can occur within a few days after infarction in patients who are not in shock and who have no enlargement or dilatation of the heart and little evidence of stasis thrombosis is best ac*counted for by* an intense thrombotic tendency in the damaged endo

cardium The more acute this damage, the greater the tendency A Jordan et al[13] demonstrated the incidence of thrombi is less in healed infarctions

Why left ventricular thrombosis should have no apparent correlation with auricular fibrillation although it is so strongly associated with congestive heart failure in which the arrhythmia frequently occurs, is not readily explained Probably the relationship would appear in a larger series

SUMMARY

Although auricular fibrillation appears to be the closest correlate of left auricular thrombosis in rheumatic heart disease it does not seem

TABLE 14—*Differences in the Mechanism of Formation of Mural Clots in the Left Auricle and in the Left Ventricle*

	Left auricle	Left ventricle
Etiology	Rheumatic heart disease	Nonrheumatic heart disease
Character of stasis	Prolonged stasis needed	Only short period of stasis needed
Mechanism of stasis	Mainly obstructed outlet	Nonobstructed-congestive heart failure aneurysmal dilatation (early exertion after myocardial infarction)
Lesion in wall	Not obvious Often microscopic No clots with acute lesions	Usually obvious Recent or old infarction Recent large lesions form more clots than old small lesions
Chamber	Usually dilated noncontracting wall	Dilatation not necessary—chamber has contracting wall
Clinical correlation (1)	Auricular fibrillation most important correlate	Auricular fibrillation not a correlate
Clinical correlation (2)	Congestive failure not a correlate	Congestive failure a definite correlate
Type of clot	Frequently small and unattached in appendage or larger—as a ball thrombu	Attached to wall No ball thrombi

to contribute to any of the necessary factors for thrombosis—auricular endothelial damage, greater coagulability of the blood or (except in a slight degree) retardation of blood flow It is a reflection of the prolonged duration and not the degree of stasis Occurring in older patients with older heart disease and with prolonged stasis it indicates the greatest probability and highest degree of stasis, coagulability, and endothelial damage

Although these same factors are present in arteriosclerotic heart disease they arise from an entirely different set of causes The character of the endothelial lesions is of dominant importance Blood coagulability *may be normal for the patient's age and sex and stasis (congestive* heart failure) is important chiefly in thrombosis associated with healed infarcts

The differences in the mechanism of formation of clots in the left *auricle and left ventricle are summarized in* TABLE 14

6 *Pathogenesis of Systemic Arterial Embolism in Heart Disease*

MOBILIZATION OF CARDIAC MURAL THROMBI

THE FORCES that tend to expel thrombi from the heart chambers are essentially the same ones that normally tend to prevent their formation. Certain humoral factors, probably fibrinolytic, conceivably may alter the character of thrombi or possibly lessen their consistency, but mechanical forces seem to be more important: an active blood flow plus the contractions of the chamber wall.

In the normal heart the force of perhaps primary importance is an active blood flow. Any motion in a liquid is transmitted to all its particles, keeping them in motion in relation to each other and to the solid material containing them. In fluid mechanics this is termed "shearing stress" and increases with the velocity of the flow.[63] Conversely, any slackening in flow reduces the shearing stress. A retarded blood flow increases the tendency both to form thrombi and to retain them at a favorable site. The chamber wall may contract actively or sluggishly or be dilated and relatively inert, so that in the left auricle during mitral stenosis with auricular fibrillation the wall may, as Soderstrom implies,[3] be as defenceless against thrombotic deposits as a horse should be against flies without his cutaneous muscles. The left ventricle may contract weakly as a whole, or there may be localized areas of weakened contraction, or actual loss of contraction as in aneurysmal dilatation.

Expulsion of thrombi from a cardiac chamber is affected by a third mechanical factor—the relation of the size of the thrombus to the size of the orifice through which it must pass. If a thrombus larger than the orifice of egress is loosened, it may become lodged in the opening either momentarily (causing syncope) or longer (causing death). The orifice of egress of the left ventricle infrequently is narrowed (aortic stenosis is infrequently associated with left ventricular infarction), but one of the main correlates with formation of left auricular thrombi is a narrowing of the mitral orifice; the ball thrombi of the heart are predominantly in the left auricle. There are of course many differences

in the interplay of factors in the mobilization of thrombi from the left auricle and the left ventricle

MOBILIZATION OF THROMBI FROM THE LEFT AURICLE

The factors affecting mobilization in the left auricle, in addition to flow, are the contraction of the body and appendage and a possible distortion of the auricular wall coinciding with ventricular systole and diastole Normally, these forces are strong and effective, but in the rheumatic heart with thrombi they are obviously ineffective at least in preventing thrombosis

During the half second of ventricular diastole a normally patulous mitral valve allows a somewhat varying rate of inflow—rapid both in the early part of diastole and in the final one tenth second—during which both the auricular appendage and the body contract however in the intervening diastasis the flow is hardly greater than the return of pulmonary venous blood to the heart This unevenness in flow *exerts an intermittent shearing stress on the wall of the left auricle and* normally tends (presumably) to prevent the attachment of platelets to even a favorable endothelial surface There is possibly a pull on the auricular wall with ventricular systole and the suction effect of ventricular diastole These are merely presumptive in man Prinzmetal *et al*[106] have demonstrated a distorting effect of ventricular systole at times in the heart of a dog an action not yet observed in man The movement of the auriculoventricular valve toward the apex with systole may induce an auricular pull[108] A diastolic suction effect has been demonstrated in the heart of the dog and turtle[35, 144] A diastolic suction effect if present in man no doubt differs in nature and degree in normal rhythm and auricular fibrillation

Effect of Rheumatic Mitral Stenosis

In rheumatic mitral stenosis with auricular fibrillation—the condition *in which four fifths of left auricular thrombi are found—all the anti*thrombotic forces are lessened First the dilated auricle accommodates a large stagnant residual pool which even with a normal valve would be evacuated only slowly Second the flow through the mitral valve is *not* the normal pulsatile flow with varying rate—it remains even and steady *throughout ventricular diastole with less tendency to produce a* shearing stress on the blood Third the auricle itself if inert through distention is unable to expel the stagnant blood through effective con

traction (At cardiotomy the auricle appears motionless.) Fourth, the presumed distorting action of ventricular systole might have less effect on a dilated and distended auricle that is subject to greatly increased internal pressure. In pure mitral stenosis, as observed at operation, there is no visible distorting motion of either the auricle or its appendage on ventricular systole or diastole.

If left auricular thrombi form, they have done so through the loss or reduction of the mechanical forces that normally prevent their formation. If these thrombi eventually are mobilized, obviously it must be by an increase in those same factors which have failed to prevent their formation. There must be either (1) a change in the character of blood flow tending to increase the shearing effect on the thrombi in the auricle and to move loose thrombi from the appendage into the active current, (2) a return of contractility to the auricle or the inert appendage, or (3) an increase in the distorting effect of ventricular systole and diastole upon the auricle.

Dislodgement of a thrombus depends to some extent on the tenacity of its attachment to the wall, which apparently varies with the age of the thrombus. Soderstrom[3] found that the clots in the body of the left auricle were usually large flat formations, broadly and firmly attached to the endocardium. He considered these "surface thrombi," as he termed them, evidence of an old chronic thrombotic state. He never encountered a recent thrombus in the body of the left auricle. Such tough fibrous thrombi are often observed at mitral valvotomy. Quite different are the red, smooth and round thrombi characteristically found in the auricular appendage. They are of recent formation and frequently unattached, and if so, the only factor preventing mobilization is stasis.

The greatest danger of embolism is from these red and recently formed left auricular thrombi. Belcher and Somerville[70] found that emboli almost always consist of a red thrombus which has become dislodged before organization has had time to start. Kuzman, Griffith Jones and Meyer[146] found, too, that fresh thrombi and not old organized clots are the source of emboli. If the red and recently formed thrombus is not discharged early into the arterial circulation it becomes attached and fibrotic.

The crucial time determining whether a clot remains a thrombus or becomes an embolus, therefore, is shortly after its formation, when it

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The crucial time determining whether a clot remains a thrombus or becomes an embolus therefore is shortly after its formation when it

will either become attached, organized and relatively innocuous, or become loose and be ejected as an embolus.

Apparently as long as the mitral valve is of normal width or widened as in mitral regurgitation any minute thrombi that may form are carried by the force of the blood flow through the patulous valve. Stagnation due to stenosis not only favors thrombosis but allows time for a clot to increase to a size that makes evacuation through the small orifice impossible. The contraction of the wall of the cul de sac (the appendix) either diminishes or ceases and the clots are retained. Ball valve thrombi rarely form except in predominant mitral stenosis. In regurgitation, if larger thrombi do form, the relatively rapid movement of blood and the larger orifice still favor early expulsion, the *bidirectional fluctuations occurring during the cardiac cycle more* effectively "milk" the left auricle than does the relatively retarded nonfluctuant unidirectional flow of mitral stenosis and apparently a high proportion of clots are expelled.[1, 4]

Effect of Rhythm

There is no evidence that either normal rhythm or established auricular fibrillation is more likely to mobilize left auricular thrombi. Among 72 patients with cerebral embolism and rheumatic mitral stenosis Harris and Levine[103] found nearly four times as many patients with auricular fibrillation as with normal rhythm and Haimovici[105] found an even greater incidence of fibrillation in 92 patients with systemic arterial embolism. Nevertheless this preponderance is not related to fibrillation itself. It is entirely in proportion to the incidence of left auricular thrombi.

Certain changes in heart rhythm however occasionally are associated with discharge of emboli. In the change from auricular fibrillation to normal rhythm the coincidence of conversion and embolism is at times evidence of a causative correlation. The reverse however is apparently as frequent—embolism coinciding with either a paroxysm of auricular fibrillation or the onset of established fibrillation. Among 153 conversions of auricular fibrillation to normal rhythm studied by Sokolow and Ball[7, 4] only two had emboli at the time of conversion but seven *had emboli at the time of a subsequent relapse from normal rhythm to* auricular fibrillation. Embolism occurred during paroxysms in five of 13 patients studied by the author.[11] Other workers have also observed this correlation.[4, 109, 198]

Sudden acceleration of the heart beat irrespective of the mechanism generally is considered capable of dislodging cardiac mural clot. Clinically however there is no evidence that sinus tachycardia, auricular flutter or paroxysmal supraventricular tachycardia is associated with any greater frequency of systemic arterial embolism. Embolism rarely occurs during auricular flutter regardless of the type of heart disease.[168, 188]

Effect of Exertion

In mitral stenosis although exercise increases pulse rate, left auricular pressure (pulmonary capillary pressure) and the rate of mitral valve flow (in cc per second of diastole), the cardiac output is only slightly increased.[99]

There is no convincing clinical evidence that effort increases embolism in rheumatic heart disease. On the contrary, Sprague and Westinghouse[39] found that of 77 arterial occlusions (presumably embolic) occurring in 38 patients with rheumatic heart disease and auricular fibrillation *more* than 90 per cent occurred during ordinary daytime activity and rest. Exertion preceding embolism, they concluded, was coincidental.

Effect of Digitalis

The stimulation of digitalis might be expected to contribute to the mobilization of left auricular thrombi although the chief effect of the drug is on ventricular contraction, which becomes slower and stronger. There is no crucial study on this question.[illegible] The long accepted theory that embolism associated with a change in rhythm from auricular fibrillation to normal is caused by a return of contraction of the auricle is open to doubt. There are several objections. First, the dilated auricle associated with auricular fibrillation has not been shown to contract if the rhythm is converted to normal. If the dilated auricle of mitral stenosis contracts more effectively with normal rhythm than with auricular fibrillation it is difficult to explain several other discrepant facts. Why should embolism occur as frequently, if not more frequently, with change from a normal rhythm to that of auricular fibrillation or from a more actively contracting auricle to one less actively contracting? Why do both direct and indirect visualization of left auricular movement fail to show differences in contraction? At cardiotomy both the body and the appendage of the auricle are inert to ordinary vision

Without inspecting the movement of the ventricle the rhythm of the auricle cannot be stated Soloff et al [7] failed to observe by angiocardiography any appreciable variation in the size of the left auricle during the cardiac cycle in patients with mitral stenosis whether the rhythm was normal or that of auricular fibrillation Any alteration of auricular contraction would not seem as significant as the abrupt change in the pattern of ventricular contraction Whether this sudden alteration in ventricular rhythm brings about mobilization of auricular thrombi is speculative Conceivably it might do so by some change in the distorting effect on the auricle of ventricular systole and diastole The nature and degree of the auricular wall pull during systole, and of a suction effect during diastole although presumptive actions undoubtedly vary with the regular and irregular ventricular contractions of normal rhythm and auricular fibrillation A sudden change in rhythm can as logically, if not more logically, explain dislodgement of an auricular thrombus than a change in auricular contraction Final explanation must await further evidence

ARTERIOSCLEROTIC HEART DISEASE

In contrast to the better documented picture of left auricular thrombosis and systemic arterial embolism in rheumatic heart disease less can be adduced with certainty about arteriosclerotic heart disease—primarily because the diagnosis itself except in cases of myocardial infarction or angina pectoris, is less frequently established with certainty and secondarily because it is more difficult to determine whether a given occlusion is thrombotic or embolic

Rheumatic heart disease is fairly often mistaken for arteriosclerotic heart disease and when the two conditions coexist the rheumatic condition is even more likely to be overlooked, together with its contribution to any embolism that may occur It rarely happens though that the arteriosclerotic condition is mistaken for the rheumatic

Most studies of systemic arterial embolism in arteriosclerotic heart disease merely state the diagnosis without detailing the studies made to assure that the diagnosis is correct and especially to rule out coexisting rheumatic heart disease A typical instance in which an error would have been made without a careful differential examination is that reported in CHAPTER 7 (case 5) Although the patient was 68 years old rheumatic heart disease was diagnosed because of disproportionate left

TABLE 15—*Left Auricular Thrombosis in Acute Myocardial Infarction*

Author	Patients	Number with left auricular thromb[o]si	Per cent with left auricular thromb[osi]
Soderstrom	181	19	10
Jordan	210	11	5
Total	391	30	7 (av

auricular enlargement in the absence of congestive heart failure While she was in another city embolism to the cerebral and femoral arteries occurred and the physician there ascribed it to arteriosclerotic heart disease

When the frequency of such errors is considered it seems quite likely that the incidence of left auricular thrombosis in arteriosclerotic heart disease is even smaller than the 8 per cent currently estimated (TABLES 15–16) and that the proportion of emboli arising from the left auricle must then be still smaller To explain systemic arterial embolism in arteriosclerotic heart disease therefore we must chiefly explain the mobilization of thrombi from the left ventricle Since there is seldom any valvular obstruction to their egress (ball thrombi do not occur in the left ventricle) the inquiry must concern itself with the mechanism by which thrombi are detached from the ventricular wall presumably a certain type of contraction Since clots form in

TABLE 16—*Left Auricular Thrombosis in Chronic Arteriosclerotic Heart Disease (Healed Myocardial Infarction Coronary Artery Disease with Hypertension and Hypertensive Cardiovascular Disease)*

	Patients	Number with left auricular thrombosis	Per cent with left auricular thrombosi
Healed myocardial infarction (Jordan)	117	3	2
Coronary sclerosis plus hypertension (Soderstrom)	274	25	9
Hypertensive cardiovascular disease (Soderstrom)	57	10	17
Total and average	448	38	8 4

the presence of a certain contracting mechanism or force, a change in the contracting mechanism would seem to be the most probable cause of their detachment

MOBILIZATION OF LEFT VENTRICULAR THROMBI

Rapid and regular ventricular contractions would seem likely to favor the mobilization of thrombi but in acute myocardial infarction where left ventricular thrombi are known to be frequent, there is no documented correlation of systemic arterial embolism with sinus tachycardia auricular flutter or supraventricular tachycardia—all of these being conditions that give rise to accelerated but regular ventricular contraction I observed no embolism in 19 cases of myocardial infarction with auricular flutter, nor in eight cases with supraventricular tachycardia[9, 10] In arteriosclerotic heart disease there is no correlation of embolism with auricular flutter[108, 188]

If such rapid heart rates do not induce embolism exertion could hardly be expected to make a difference

The effect of rapid irregular ventricular contraction such as is associated with auricular fibrillation is more difficult to evaluate—primarily because of the unreliability of diagnosis of the underlying disease in studies on arteriosclerotic heart disease secondarily because of the previously mentioned doubt as to whether a given occlusion is thrombotic or embolic and further because digitalization almost always practiced in auricular fibrillation may theoretically contribute to mobilization of clots

If the number of ventricular thrombi formed is no greater in auricular fibrillation (see CHAPTER 3) any increase in embolism must be due to greater mobilization of thrombi The irregular contractions of the ventricle *secondary to auricular fibrillation might tend to loosen the* attachment of a ventricular clot more readily than the even contractions of normal rhythm If systemic arterial embolism occurs soon after *auricular fibrillation begins the change in contractions might be suspected as a cause* If fibrillation has been going on for some time before embolism occurs it is questionable whether the clot could have been *mobilized solely by an arrhythmia that did not prevent its formation*

Two ways have been suggested in which digitalis may contribute to systemic arterial embolism in arteriosclerotic heart disease At least *theoretically*," *Fishberg Hitzig and King* [3] *point out* digitalis pre

di poses to certain dangers in myocardial infarction Notable among the e are mobilization of ventricular mural thrombi in con e quence of a more powerful systole Whether these dangers are actual can only be established by observation of a large series of cases The econd theoretical danger from digitalis po tulated for patients with congestive failure is the decrea e in heart size which al o might tend to di lodge thrombi [34 35] Blumer [4] warned The frequency with which thrombi are present in coronary occlusion ju tifies the attitude of many phy icians regarding the avoidance of medication with digitalis unle s there is ome very definite indication for its use such as auricular fibrillation

In acute myocardial infarction where diagnosi of arteriosclerotic heart di ease is highly accurate and diagnosis of s temic arterial embolism reasonably accurate the incidence of auricular fibrillation is so low that it is difficult to obtain a large series

Some years ago I tudied a group of 84 patients with auricular fibrillation occurring in acute myocardial infarction [15] This tudy was made prior to the use of Dicumarol eliminating an important antithrombotic factor The relation of auricular fibrillation to sy temic arterial embolism in this group is intere ting The diagno is of acute infarction was reasonably certain (typical EKG evolution) and that of sy temic arterial emboli m highly *probable* (patients with sudden hemiplegia or udden occlusion of an extremital artery) Forty-eight patients had congestive failure and 36 did *not*

The variables affecting arterial thromboemboli m in acute myo cardial infarction are so many that nothing more than indications are ju tified in evaluating the mobilizing force from statistical data The ize of the acute infarct and the presence or ab ence of congestive failure are the factors chiefly affecting the formation of thrombi Auricular fibrillation and the use of digitalis are the theoretic factors in mobilizing thrombi that need evaluation

If one tudies a group with acute myocardial infarction and conges tive heart failure in order *to e — e the effect* of auricular fibrillation and digitalis the results are interesting if not convincing Auricular fibrillation was associated *with a significant* increased incidence of sy temic arterial emboli m—see TABLE 17 ($P \leq 0.01$) In a tudy of those patients with an acute myocardial infarct conge tive heart failure and auricular fibrillation made to determine the incidence of sy temic arterial emboli m among those receiving and those not receiving digi

TABLE 17—*Incidence of Systemic Arterial Embolism in Patients with Acute Myocardial Infarction and Congestive Failure in Those with Normal Rhythm and Those with Auricular Fibrillation*

	Number of patients	Per cent with systemic arterial embolism
Normal rhythm	85	7 (6 patients)
Auricular fibrillation	48	27 (13 patients)

talis, there was a suggestive and possibly significant increase in those who received digitalis (TABLE 18—P=0 04)

The data in this study are admittedly suggestive and certainly heuristic There is too a critical need for more facts What is pointed up are *the difficulties involved in evaluating the relation of auricular fibrillation* to arterial embolism in arteriosclerotic heart disease If the effect of the arrhythmia is inconclusive in a group in which the diagnosis both of the heart condition (acute myocardial infarction) and of the systemic arterial embolism is highly accurate (the embolic episodes were typical either sudden attacks of hemiplegia or sudden peripheral occlusions), then how conclusive can studies be in patients with supposed chronic arteriosclerotic heart disease in whom the diagnosis of both the heart disease and the cause of arterial occlusion is less certain? If the effects of the arrhythmia in acute myocardial infarction cannot be divorced from the effect of digitalis how can systemic arterial embolism in arteriosclerotic heart disease be ascribed to auricular fibrillation unless the effect of digitalis be excluded?

In rheumatic heart disease auricular fibrillation can be definitely correlated with an increased incidence of both left auricular thrombosis and systemic arterial embolism In arteriosclerotic heart disease there

TABLE 18—*Incidence of Systemic Arterial Embolism in Group of 48 Patients with Acute Myocardial Infarction with Congestive Failure and Auricular Fibrillation in Those Given Digitalis and Those Not Given Digitalis*

	Number of patients	Per cent with systemic arterial embolism
Group given digitalis	39	33 (13 patients)
Group given no digitalis	9	0 (no patients)

is no conclusive evidence that auricular fibrillation is associated with an increased incidence of left sided thrombi nor is there conclusive evidence that any apparent increased incidence in systemic arterial embolism attributed to auricular fibrillation cannot be correlated equally well with the administration of digitalis in those with congestive heart failure

SUMMARY

There is no adequate explanation for the mobilization of left auricular thrombi in the majority of instances The occurrence of embolism cannot be correlated with anything save occasionally a change in the rhythm of ventricular contraction from a regular to an irregular rhythm or vice versa An increase in ventricular rate alone if regular does not increase the incidence of embolism There is no evidence either that exercise tends to increase the mobilization of left auricular thrombi nor is there correlation of embolism with a regular tachycardia such as sinus tachycardia auricular flutter or paroxysmal supraventricular tachycardia

TABLE 19—*Mechanism of Mobilization of Left Auricular and Left Ventricular Mural Clots*

	Left auricular	Left ventricular
Immediate mobilizing factor	Related to type of flow not contraction of auricular wall	Related more to contraction of ventricular wall
Relation of arrhythmias 1 Regular tachycardia	No correlation	No correlation
2 Rapid irregular rhythm —auricular fibrillation	No correlation with established rhythm	No correlation with established rhythm
3 Sudden change of rhythm—normal to auricular fibrillation or auricular fibrillation to normal	Occasional, but definite	Not enough evidence
Digitalis	No correlation	A suggestive correlation but not enough evidence
Exertion	No correlation	No correlation

Mobilization of left auricular thrombi in rheumatic heart disease therefore must be regarded in the main as a fortuitous event

Mobilization of a left ventricular thrombus occurs if a clot is detached from the wall None is retained as a ball thrombus A change in the contraction of the wall probably accounts for the dislodgement There is no demonstrable correlation with rapid, regular ventricular contraction and any correlation with auricular fibrillation is complicated by the consistent use of digitalis Digitalis induces two changes in the contractile mechanism possibly conducive to the evacuation of left ventricular thrombi (1) a more powerful systole and (2) a reduction in size of the left ventricular cavity

A summary of the mechanism involved in the mobilization of left sided cardiac mural thrombi is given in TABLE 19

7 Differential Diagnosis of Rheumatic and Arteriosclerotic Heart Disease

RHEUMATIC HEART DISEASE and arterio clerotic heart disease differ in the danger of sy temic arterial embolism which they *present and in* the criteria determining whether and what prophylactic antithrombotic mea ures are indicated In this connection it is crucially *important to* recognize rheumatic heart di ease because (1) it probably accounts for most sy temic arterial embolism (2) it is unrecognized *during life* even in a high proportion of patients with gro s mitral *valvula disease* (3) by excluding its possibility the diagnosis of arterio clerotic heart di ease can be more confidently made and acted upon and (4) the treatment is by no m ans the same even *during congestive heart failure*

Whereas coronary arterial di ease may remain undetectable until it manifests itself in acute myocardial infarction or *pr m y angina pec toris* hypertensive cardiovascular disease *usually* is not difficult to diagnose Rheumatic heart di ease if suspected hould be diagno able in mo t in tances if not always during life and before it causes serious di ability

Important procedures for differentiation between rheumatic and arteriosclerotic heart disea e include *auscultation in the left lateral* po ition roentgenograms (*not merely fluoro copy*) in the postero anterior right oblique and left lateral po itions and electrocardiography Dotter[80] has empha ized the *importance* of roentgenograms in addition to fluoroscopy to determine enlargement of cardiac chambers

INCIDENCE OF UNSUSPECTED RHEUMATIC HEART DISEASE

The incidence of un uspected rheumatic heart disease in all degrees i probably enormous Fa shender[7] Hall and Anderson[106] and others have hown that its minor tigmas *occur* in a large proportion of per sons and Lichtman and Mast r[14] *found* gross rheumatic valvular damage at necropsy in 52 per cent of 342 patients over 50 years old with anatomic evidence of heart di sease More important these gross valvular deformities are often *unrecognized* during life Although

rheumatic heart disease is often wrongly diagnosed as arteriosclerotic heart disease; for example, in 15 of 50 cases that Kaufman and Poliakoff [14] found at necropsy; the reverse error seldom occurs. Similarly when the two conditions coexist, arteriosclerotic heart disease is usually recognized and rheumatic heart disease overlooked. According to Gardner and White [83] the coexistence was recognized in only 7 of 32 cases. Arteriosclerotic heart disease was missed only five times but rheumatic heart disease 21 times.

PATHOLOGIC STAGES OF RHEUMATIC HEART DISEASE

Five fairly definite stages of rheumatic heart disease preceding clinical embolism may be recognized pathologically (FIGS. 8–12). These

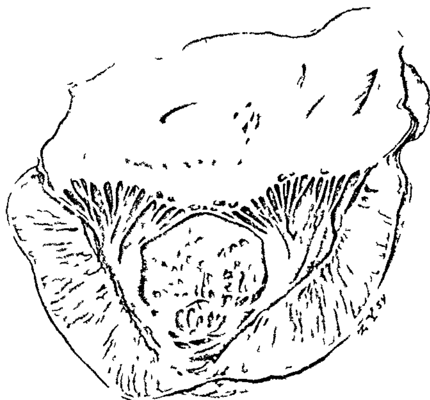
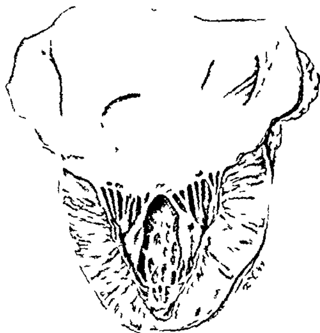


FIG. 8. Stage 1. Acute rheumatic carditis. Rheumatic verrucae on valve margins. Thickened corrugated patch of auriculitis on posterior wall of auricle.

overlapping tages cannot be eparatel) identified clinicall) in every patient but hould be u pected and earched for

Stage One Acute rheumatic carditis ma) not be recognized but when it i involvement of the left auricle i pre umed (FIG 8)

Stage Two Progre ive change in the mitral valve and the left auricle result in deformity of the mitral valve cau ing steno i regurgitation or b th With increa ing teno i there is u uall) a concomitant dilatation of the left auricle to an unpredictable degree— light moderate or marked (FIG 9)



Fi 9 Sta 2 Progre ive anat mical changes with narrowing of mitral orifice and auricular dilatation with beginning ta i Chordae tendineae h rtened and thi kened Per i ten t at h of auriculiti

Stage Three Maximal deformity of the mitral valve and maximal dilatation of the left auricle probably are reached in ten to fifteen years (FIG 10)

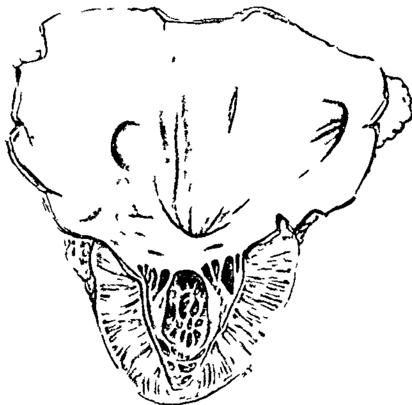


FIG 10 Stage 3 Maximal stenosis of valve and maximal dilatation of auricle Marked dilatation of auricle Persisting auriculitis

Stage Four The formation of thrombi is followed eventually by mobilization of approximately 50 per cent (FIG 11)



FIG 11 Stage 4 Formation of left auricular thrombi following prolonged stenosis and auricular [illegible] auricle dilated Small thrombi at site of auriculum and between trabeculae carneae in the auricular appendage

Stage Five Minor and usually unrecognized systemic arterial embolism (FIG 12)

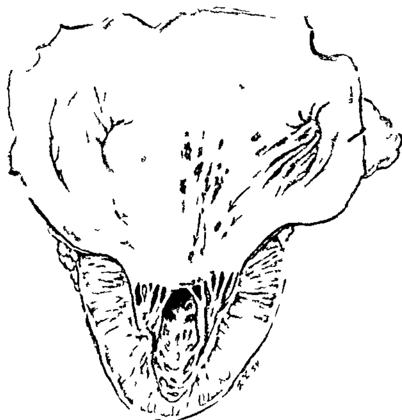


FIG 12 Stage 5 Mobilization of small thrombi as emboli usually unrecognized

Stage Six Obvious serious embolism (FIGS 13–15) which may be quickly fatal



FIG 13 Stage 6 Stage of mobilization of large thrombi as major recognized systemic arterial emboli



Figs 14–15 (shown side by side) Steno i of mitral orifice and thrombo i of left auricular appendage producing emboli m to abdominal aorta with resulting gangrene of both lower extremitie (*By permi ion from Gould The Pathology of the Heart* Springfield Ill Charles C Thoma 1953 chap 8 [Dr A H Baggen to s] p 668)

CLINICAL DIAGNOSIS OF RHEUMATIC HEART DISEASE

Important to the clinical diagnosis of rheumatic heart di ea e is the recognition of two preceding phases The first i an acute upper re pir atory infection with an as ociated streptococcal pharyngitis In about three per cent of the patients with Group A beta hemolytic streptococci acute rheumatic manife tations with endocarditi occur after a latent period (a few days to six weeks) It is impo sible however always to recognize an upper respiratory infection as streptococcal and cau ative of rheumatic fever or to diagno e the acute rheumatic condition the econd phase from its signs and symptoms

As the direct cause of rheumatic fever is not known and cannot be tested for the diagnosis must be based on the relative importance of whatever major or minor findings are present and therefore can only be presumptive In childhood the disease frequently meets the accepted criteria established by Jones[139] Rigid as these criteria are they admittedly exclude a certain proportion of cases of true rheumatic fever and it is felt that the imposition of lifelong penicillin administration based on a false diagnosis is a greater hardship than the possible sequelae in the event of unrecognized rheumatic fever

After adolescence the diagnostic problem is far more complex Acute rheumatic infection both in the original attack and in recurrent episodes is frequently missed Jones major criteria for diagnosis are rarely satisfied in the adult and the minor features are either absent or of doubtful significance There are thus few clinical findings to warn of impending rheumatic carditis Many middle aged patients in the chronic stage of rheumatic heart disease give no history of preceding streptococcal infection or of rheumatic fever Such was the case with 52 per cent of 324 middle aged patients studied by Rosenthal and Feigin (32 cases)[267] Sprague and Carmichael (115 cases)[231] Appel and Kossman (71 cases)[8] and Hebbert and Rankin (106 cases)[113]

Causes of Error in Diagnosis

There are several causes of failure to diagnose more than one third of all cases of rheumatic heart disease during life First a physician may not see the patient or if so only late in life The disease often runs a benign course giving rise to no characteristic signs or symptoms before death results from another cause or symptoms may not occur until late in life giving the physician no opportunity for early diagnosis A well known instance of benign mitral stenosis unrecognized until old age is that of Dr Herman Vickers described by White and Bland [illegible] Most of the unrecognized cases have however been seen for the first time in middle age The main and correctible cause of missing the diagnosis of rheumatic heart disease in patients who have not previously seen a physician is the frequent failure to suspect and search for it in persons past 40 years of age except when findings definitely point to it. The emphasis placed upon rheumatic heart disease as essentially a condition of younger persons has obscured its high incidence—in all degrees of severity—in the middle aged and elderly Rheumatic



FIGS 14–15 (hown ide by side) Stenosis of mitral orifice and thrombosi of left auricular appendage producing emboli m to abdominal aorta with resulting gangrene of both lower extremitie (By permi sion from Gould s *The Pathology of the Heart* Springfield Ill Charle C Thoma 1953 chap 8 [Dr A H Baggen to s] p 668)

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Whether associated with auricular fibrillation or with normal rhythm rheumatic heart disease in middle age is unrecognized with about equal frequency The problem is to detect or to exclude rheumatic heart disease when no previous sign is given The cases reported in this chapter illustrate how many have been erroneously treated because a careful differential diagnosis was not made In some the diagnosis was made only because embolism forced its consideration and in others because our former mistakes had taught us always to apply the direct query Have we excluded rheumatic heart disease? Only by adhering to this precaution can rheumatic heart disease in middle age be found and treated

Diagnosis of Mitral Stenosis

The most reliable criteria for the diagnosis of mitral stenosis are auscultatory and roentgenologic findings Electrocardiograms are at times of value in directing attention to the lesion It cannot be too strongly emphasized that auscultation is frequently the only means of diagnosis and often the characteristic diastolic murmur can be elicited only with the patient on his left side Careful auscultation in this position with the breath held after expiration should be routine in the examination of all patients in whom heart disease is suspected Too frequently this is not done In the following four cases embolism occurred before a diagnosis of rheumatic mitral stenosis was made In three the characteristic murmur had not been heard before embolism probably because a careful search was not made In the fourth the patient had not seen a physician before the embolism occurred

Case 1 —A 62 year old housewife had been well until about five weeks before examination At that time she had felt fatigue and shortness of breath and had been given digitalis When first seen in December 1930 she was moderately dyspneic with a vital capacity of 3 liters A totally irregular heart beat was shown by electrocardiography to be auricular fibrillation with premature beats No murmurs were noted but no examination in the left lateral position was made Under treatment the compensation returned but the auricular fibrillation persisted The blood pressure was 130/80 Roentgenogram of the heart showed slight enlargement of the left ventricle but no evidence of enlargement of the left auricle The tentative diagnosis was arteriosclerotic heart disease auricular fibrillation and congestive heart failure until two subsequent episodes were considered possibly attributable to embolism On one occasion there was severe pain in the right costovertebral angle On the other occasion the patient suddenly had double vision could not walk straight and had to lean against a car

heart disease, unless obvious, is usually diagnosed as arteriosclerotic heart disease.

The correct diagnosis of heart disease in middle age will be made more often if rheumatic heart disease is considered a presumptive diagnosis in every cardiac patient, *either alone or as an associated condition*, until proper studies have been made to exclude it.

Auricular Fibrillation in Middle Age

If auricular fibrillation is seen for the first time in middle age or later, without obvious etiologic findings and no reliable history is *obtained of acute rheumatic fever or acute rheumatic carditis*, the arrhythmia more often than not is diagnosed and treated as nonrheumatic heart disease unless a critical differential study is made. A history *of rheumatic fever would be of help*, but as noted above the acute stage is missed in the majority of patients. Moreover, a careful inquiry regarding a past medical history of the various manifestations of rheumatic fever usually is not made. The questioning frequently is cursory, indifferent and unrewarding. I have also been frequently remiss (Case 7). It is of more than academic interest, however, to distinguish between rheumatic and nonrheumatic heart disease as the cause of auricular fibrillation. The indicated treatment can vary in many essential and critical detail. Several specific measures may be indicated if rheumatic heart disease is the cause: continuous prophylaxis against recurrent streptococcal infection, mitral valvoplasty if mitral stenosis is present, and antithrombotic measures if embolism occur.

When auricular fibrillation is associated with rheumatic mitral stenosis, the probability both of primary and of recurrent systemic arterial embolism is significantly greater than when associated with chronic arteriosclerotic heart disease. The basis for *probability* in either case is the incidence of thrombi in the left auricle or ventricle. If auricular fibrillation occurs in association with rheumatic heart disease, the chance of a *left sided thrombus varies from 50 per cent* in general to about 75 per cent if pure mitral stenosis present.[36] In arteriosclerotic heart disease the chance is only about 33 per cent, and is no greater *in auricular fibrillation, as evidenced by two studies*.[1, 8] In neither of these groups did auricular fibrillation increase the incidence of left sided clots. In chronic nonrheumatic heart disease, in fact, there is an *entirely different correlation: the left sided thrombi* are associated chiefly with congestive failure.

auricle The electrocardiogram showed normal sinus rhythm and notched P waves The patient gave a history that included an episode in July 1954 characterized by (his wife said) mental confusion some incoordination in walking and slight dysarthria The symptoms were transitory and he did not consult a physician At the age of nine he had had an attack of acute rheumatic fever but a diagnosis of rheumatic heart disease had never been made

Potentially serious embolism (Cases 1–4) thus may be the first evidence both of left auricular thrombosis and of the underlying rheu

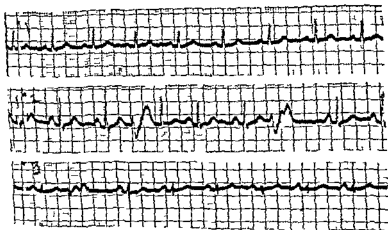


Fig 16 Tracing showing abnormal bifid P waves in lead ?

matic heart disease The discovery then may be at the cost of *hemiplegia* the loss of a leg or death The mortality *due to* emboli m in middle aged patients with rheumatic heart disease is high[113] Unfortunately although the greatest danger follows the onset of *auricular* fibrillation the arrhythmia frequently causes the characteristic *murmurs* to disappear the early diastolic the mid diastolic and particularly the presystolic The *murmur may be atypical* in quality intensity or timing[108] Probably it is because of this *masking* that mitral stenosis as a cause of auricular fibrillation was estimated by two authors as only 36 per cent in 79 cases[103, 17] The proportion is probably too low

Roentgenologic Study

Many of the mistakes in diagnosing rheumatic heart disease as arteriosclerotic heart disease in middle age could possibly be avoided if a

for 15 minutes before she could proceed After this second episode embolism was suspected and auscultation at the apex in the left lateral position revealed a definite low pitched diastolic murmur More careful questioning revealed that she had rheumatism of the knees in childhood The diagnosis was changed to rheumatic mitral stenosis with left auricular thrombosis and systemic arterial embolism

In a Cabot case report from the *New England Journal of Medicine* it will be noted that embolism preceded the observation of a late diastolic murmur typical of mitral stenosis [4]

Case 2—A 66 year old housewife had for three months palpitation skipping heart and moderate dyspnea on climbing three flights and she had been receiving digitalis When fever and upper abdominal pain developed she was operated upon for acute cholecystitis and cholelithiasis At this time ascultation disclosed a grade 2 apical systolic murmur and a totally irregular rhythm The aortic second sound equalled the pulmonic ' On careful questioning there was no history of rheumatic fever Ten days later sudden coldness and pallor developed in the right leg No pulsations were palpable below the right femoral artery Tromexan and Dicumarol were administered Two days later a cardiologist discerned a definite grade 3 mid diastolic rumble at the cardiac apex with presystolic accentuation

Case 3—Another pertinent case is that of a 64 year old engineer who had been well all his life save for a bad sore throat at the age of 31 There were no joint or muscular pains Several weeks after the attack Since that time he had worked without sick leave and had never noted shortness of breath in exertion palpitation spontaneous pain or easy fatigability One evening he noticed some weakness and awkwardness in his right hand and right leg though he walked without difficulty After a good night s sleep the leg seemed normal but the hand was weak and inept The blood pressure that day was 144/84 in the right arm and 134/84 in the left The rhythm was regular No murmurs or accentuated sounds were heard either in the upright or the supine position He was not examined in the left lateral position Because of the patient s age and the absence of cardiac murmurs the tentative diagnosis was cerebral thrombosis The next day however electrocardiograms showed abnormally prominent notched P waves in lead 2 (Fig 16) On careful auscultation with a bell stethoscope with the patient in the left lateral position a distinct and low pitched presystolic rumble characteristic of mitral stenosis was heard but only over an area about one and one half inches diameter

Case 4—Mr A F age 63 was first seen in January 1956 following two short convulsive episodes There were no previous symptoms to suggest heart disease Physical examination revealed a rough low pitched presystolic murmur at the mitral area and a cardiac roentgenogram in the right oblique position showed a straight left border and enlargement of the left

auricle The electrocardiogram showed normal sinus rhythm and notched P waves The patient gave a history that included an episode in July 1954 characterized by (his wife said) mental confusion some uncoordination in walking and slight dysarthria The symptoms were transitory and he did not consult a physician At the age of nine he had had an attack of acute rheumatic fever but a diagnosis of rheumatic heart disease had never been made

Potentially serious embolism (Cases 1–4) thus may be the first evidence both of left auricular thrombosis and of the underlying rheu

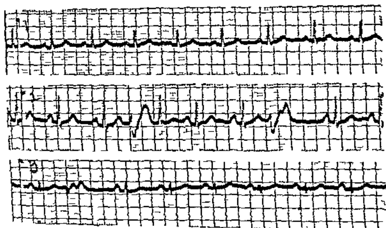


Fig 16 Tracing showing abnormal bifid P waves in lead 2

matic heart disease The discovery then may be at the cost of hemiplegia the loss of a leg or death The mortality due to embolism in middle aged patients with rheumatic heart disease is high.[113] Unfortunately although the greatest danger follows the onset of auricular fibrillation the arrhythmia frequently causes the characteristic murmurs to disappear the early diastolic the mid diastolic and particularly the presystolic The murmur may be atypical in quality intensity or timing [185] Probably it is because of this *masking* that mitral stenosis as a cause of auricular fibrillation was *estimated* by two authors as only 36 per cent in 95 cases [1 5] This proportion is probably too low

Roentgenologic Study

Many of the mistakes in diagnosing rheumatic heart disease as arteriosclerotic heart disease in *middle age* could possibly be avoided if a

roentgenologic study for left auricular enlargement were made The absence of a diastolic murmur in a patient with auricular fibrillation does not exclude rheumatic heart disease, and reliance must be placed on subsidiary findings[151] A characteristic roentgenologic pattern, together with the arrhythmia justifies a tentative diagnosis even without other findings and stimulates a more critical appraisal of signs and



FIG 17 Enlargement of the left auricle posteriorly displacing e ophagus

symptoms with earlier recognition of some of the small and less serious as well as the large serious emboli

Case 5—A 66 year old woman was injured in a fall Incidental to examination, she was found to have auricular fibrillation A diagnosis of arteriosclerotic heart disease was made On re-examination 18 months later she had noted no dyspnea other than slight shortness of breath upon climbing stairs, which she attributed to her age She felt that possibly she tired more easily than she should Auricular fibrillation was still present the blood pressure was 162/100 and the ventricular rate was 96 No diastolic murmur could be detected in the left lateral *position* A few basal lung rales were heard bilaterally There was no peripheral congestion or edema Fluoroscopy revealed *enlargement of the left ventricle and* some tortuosity of the aorta In addition roentgenograms in the right oblique and *left lateral positions* showed definite enlargement of the left auricle (Fig 11) This probably represents rheumatic mitral stenosis despite the absence *of any diastolic murmur* In September 1956 at age 70 and while traveling *she* suffered cerebral and femoral arterial embolism The *diagnosis* was arteriosclerotic heart disease

There are several differentiating points between the left auricular enlargement found in auricular fibrillation in rheumatic heart disease and that in arteriosclerotic heart disease In rheumatic heart disease the left auricle usually is markedly enlarged and there need be *no* congestive heart failure [41] The left auricle has failed because of mitral obstruction the chamber is the site of *primary failure* which precedes right heart failure In arteriosclerotic heart disease however the left auricle is enlarged only slightly to moderately the left ventricle is always *enlarged* and congestive heart failure is present The left auricular failure is secondary to left ventricular failure and subsequent to congestive failure Thus if a *left auricle* is *enlarged out* of proportion to the left ventricle and congestive heart failure is absent it is good presumptive evidence of rheumatic heart disease This was true in case 5

Case 6—When a 64 year old woman *was* seen at home for a cold her heart was found to be fast and missing She had no preceding shortness of breath palpitation *or unusual fatigue* The diagnosis of auricular fibrillation was confirmed by electrocardiogram The *blood* pressure was 132/86 No diastolic murmurs could be heard in the left lateral position either then or later The contour *of the* heart in the *right* oblique and left lateral views indicated left auricular enlargement the retrocardiac space was encroached upon the left border abnormally straight and characteristic of rheumatic *mitral* heart *disease* Inquiry brought out that the patient had frequent "rheumatic" leg aches as a child On a provisional

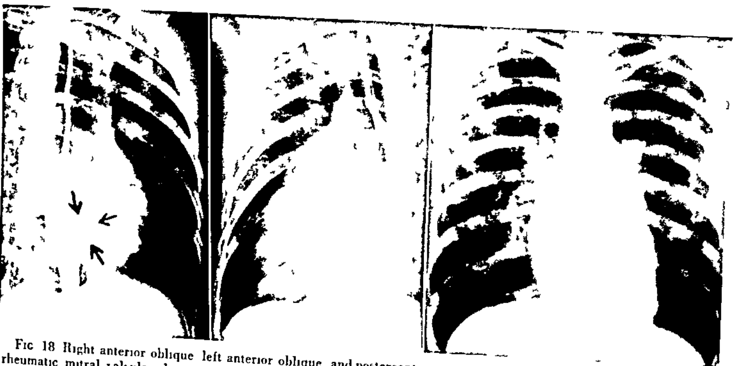


FIG 18 Right anterior oblique left anterior oblique and posteroanterior views showing calcification of mitral valve in rheumatic mitral valvular disease (Figures 18 and 19 reproduced by permission of the Department of Radiology University of Southern California School of Medicine)

dia no i of rheumatic valvuliti he will be ob erved carefully f r characters tic murmurs and evidence of minor emboli m

A clinician need not be reluctant to diagno e mitral teno is even in the ab ence of left auricular dilatation if other findings are ig nificant. He must remember that this finding is tre ed as a clue and not a prerequisite to diagnosis It is not always pre ent and even when present is not always roentgenologically evident[1]

Another roentgenographic finding however is an invariable index of mitral teno is A calcified mitral valve (as distinguished *from* calcification of the annulus fibrosus) if hown by roentgenography is considered conclusive evidence of mitral teno i whether other signs are present *or not*[93] (FIGS 18 and 19) So man e timates that 10 per cent of the patients with rheumatic mitral teno is have vi ible calcification of the mitral valve but undoubtedly it i een in only a very mall *proportion* of these patients—probably because it is not u pected and a careful *roentgenographic* examination is not made So man finds fluoroscopic examination with optimum *accommodation of the eyes* more helpful than the roentgenogram which he ay rarely adds any thing if the *fluoro copic* examination is carefully done Riebel[93] *has* recently reemphasized the preci e *preparation of the eyes* that is necessary if red goggles are used The use of hort *duration* roentgen exposure (2 to 3 millisecond) will probably be of *more diagno tic* value than fluoroscopy Dotter[94] believes

U ing radiologic findings as the basic evidence *Sosman* [9] classified patients with ubclinical *mitral* di ea e into *several* division Fir t a mall group *with unequivocal* roentgenographic *but* inconclusive clinical igns (or *none at all*) *of mitral* di ease Second the largest group tho e with definite roentgenographic findings of mitral disea e in whom the *physical signs* have not been detected *previously* by one or more competent phy ician *although they* are discernible when earched for Third *patients with roentgenographic* evidence compatible with mitral disea e but not *diagno tic* and a ociated with *no other* clinical sign

Electrocardiographic Changes

The importance of the *electrocardiogram* in patients with normal rhythm i illu trated in case 3 *Not until* the electrocardiogram was in pected was rheumatic *mitral* teno is u *pected* A definite notched P wave in the electrocardiogram *of a* patient with *a clear* history of



Fig 19 Posteroanterior right anterior oblique and left anterior oblique views showing calcification of annulus fibro us of the *mitral valve in nonrheumatic* heart disease Typical C shaped or J shaped calcification

previous rheumatic disease makes rheumatic mitral stenosis a highly probable diagnosis even in the absence of definite auscultatory or other signs Fraser and Turner [8] studying 2000 unselected cardiograms found notched P waves only twice in the absence of mitral valvular disease. Conversely the notched P wave is present in most cases of pure mitral stenosis In 115 patients with normal rhythm submitted to surgical treatment for mitral stenosis the same authors found broad or bifid P waves in 92 per cent

Presumptive Diagnosis

In certain instances a tentative diagnosis is justified on relatively few findings According to Levine and Love,[131] One can make a presumptive diagnosis of mitral stenosis in any patient with a past history of rheumatic fever if auricular fibrillation is present

Case 7—A 69 year old man had a paroxysm of auricular fibrillation which was terminated with several doses of quinidine Following this episode there was *no significant* dyspnea palpitation or fatigability The blood pressure on several observations was never higher than 150/95 *No* diastolic murmurs were audible In the subsequent five months there were several short periods of paroxysmal auricular fibrillation (of which the patient was acutely aware) relieved by quinidine and also—not associated with these paroxysms or the use of the drug—several episodes of light headedness lasting for several hours and accompanied by disturbance of the sense of balance *Fluoroscopic* examination following barium dosage gave no *evidence of* enlargement of the left auricle *After* six months of considering the diagnosis of arteriosclerotic heart disease more careful questioning disclosed *how* cursory our original investigation of the past medical history had *been* The patient had repeated attacks of "inflammatory rheumatism *in* childhood and adolescence Despite the absence of diastolic murmur or of demonstrable enlargement of the left auricle rheumatic valvulitis is considered a *more than* remote possibility because of the childhood disease and the attacks of fibrillation The spells of light headedness are possibly due to minor *embolism* and further embolic episodes will be continually suspected Even though these are only minimal criteria *for* a tentative diagnosis of *rheumatic* heart disease the patient will receive the benefit of maximal *observation*

RECOGNITION OF EMBOLISM

Perhaps the most important point *of* all in the management of systemic arterial embolism in rheumatic heart disease is the recognition of the small emboli that usually precede major embolism Proper management (CHAPTER 8) *can* enormously *reduce* future embolism The

mortality from small emboli is nil but small emboli if unrecognized and untreated are frequently and soon followed by major emboli which may kill or maim the patient

Once the diagnosis of rheumatic heart disease has been made the clinician must consider embolism in the differential diagnosis of every condition that can arise from it. Only a very small proportion of systemic arterial emboli are clinically recognized chiefly the major ones. Even then the diagnosis frequently is made late. The earlier and minor emboli may escape recognition—first because the signs and symptoms are so slight that even the patient fails to notice them, second, because the physician does not suspect their occurrence, third because minor signs and symptoms of embolism are not sufficiently investigated and last because arterial pulses are not recorded early in all patients with rheumatic heart disease

In patients with auricular fibrillation especially pain in the costovertebral angle should be considered as renal embolism and significant microscopic hematuria should be sought. Intravenous pyelograms should be made if possible since absence of renal function may identify the lesion [15]

Transitory faintness and dizziness should excite suspicion of small cerebral emboli which frequently cause the symptom [17]. In my experience the significance of most of these episodes is unrecognized

Mesenteric arterial embolism unless surgically treated is frequently fatal. Abdominal pain nausea and vomiting may be the symptoms and unless embolism is considered the patient's chance of surviving resection is imperiled. Mesenteric embolism may masquerade as acute appendicitis [9, 16, 46]

Recording Pulses

One of the most important measures for the early detection of peripheral embolism is the frequent observation and recording of pulses. By this means arterial occlusions may at times be identified even though not suspected. In the extremities impairment of arterial pulsation may be the only means of diagnosis in the absence of major signs and symptoms [10]

On suspicion of embolism pulse recording may be the confirming datum. Richards [40] declares "The idea that embolism is a condition with a dramatic onset invariably *associated with pain is one which* dies hard." Of 48 cases of peripheral embolism which he observed the

onset of 11 was marked not by sudden pain but by numbness or coldness of the extremities. Haimovici[19] carefully recorded the mode of onset in his 240 cases and found that in 28 pain or numbness and coldness developed gradually. Madoff, Thompson and Strieter[16] recorded a case where the patient had no complaints but coolness of the extremities led to the finding that pulses were absent beyond the femoral vessel. Saddle embolus of the aorta was the diagnosis.

In addition to raising the suspicion of embolism or confirming it, pulse palpation may also identify the site of occlusion, permitting a precise surgical approach. Griffiths[103] apparently recorded the first instance in which embolism to the bifurcation of the common carotid artery was diagnosed from the sudden onset of hemiplegia and coincident loss of pulsation. Holden,[116] who records a similar instance, believes that carotid embolism occurs more often than is suspected, since the carotid pulsations in the neck are seldom palpated. Dunning[61] describes a method of pharyngeal palpation to detect occlusion of the internal carotid artery. Bloomberg, Blumberg and Haimovici[6] cite a case of saddle embolism in the aortic bifurcation occurring after mitral valvoplasty in which no one could recall having felt the femoral artery pulses before operation. I have observed another case in which the same oversight led to incorrect localization of the embolus. Silbert[200] emphasizes the need for routine determination of pulses in all extremities and for constantly remembering the possibility of embolism. Since either the dorsal pedal or the posterior tibial pulses, or both, may be absent in normal persons, as Silverman and Morrison have shown,[1 2] it is obviously urgent to note this absence before there is any reason to suspect embolism. If mitral valvoplasty is to be performed, it is of great value to know whether there has been previous embolism.

The risk and difficulty of mitral valvoplasty is greatly increased if a thrombus has formed in the left auricle. When these thrombi are not suspected and special precautions not taken, there is a high incidence of embolism at the time of operation. The early recognition of embolism occurring during operation is mandatory. A patient may survive a successful operation only to succumb to a belatedly recognized saddle embolus. In many early cases peripheral arterial embolism was diagnosed only when the patient recovered from the anesthetic with a pain in the leg.[17 8]

The best method of detecting such embolism early is to record the pulses before, during and after valvoplasty, rather than to wait for

development of obvious symptoms Tropea and Entine [50] specify that the carotid pulses and those of the extremities should be recorded after the operation while the patient is in the operating room Boyd[8] makes a similar recommendation If an embolus does lodge in the common carotid artery, *and is recognized early it may prove amenable* to surgical removal For this reason it is advisable that the anesthetist feel the carotid pulse frequently throughout the operation

Madoff, Thompson and Strieter [1c] specify precise measures for determining the status of the pulses Before operation, they examine all accessible pulses and then mark with indelible ink the exact site of any pulse that is difficult to palpate so that the pul e can be rapidly checked at any time If the condition of the pulse is questionable oscillometric examinations are indicated Regarding postoperative pre cautions they reported From this time forward the status of the peripheral pulses is determined and recorded at hourly intervals for 48 hours This can be done easily and quickly by nurses as well as house officers since the location of the pulses has previou ly been es tablished " The same procedure should be observed after embolectomy which is often followed by recurrence that may go too long unrecog nized unless the pulses have been carefully recorded Klingensmith and Theis [140] report that 6 of 19 patients undergoing femoral or iliac embolectomy died in the hospital of ubsequent emboli In 27 embo lectomies reported by Taylor [44] there were seven deaths and only *four recoveries from sub equent embolism*

Angiocardiography

The knowledge that a left auricular thrombus was pre ent would alert the clinician to the high probability of emboli m *(50 per cent)*, if no operation were performed and the surgeon to the increased danger of emboli m during operation Visualization of left auricular thrombi through special angiocardiographic technics has been demon strated, but as yet is not perfected Large filling defects produced by both auricular tumors and auricular thrombi have been demonstrated [9] Steinberg [33] has seen a clear cut instance of a left atrial mural throm bus in rheumatic heart disease demonstrated by angiocardiography and verified by autopsy He wrote me that unfortunately the e films could not be located The fir t published angiocardiogram to show a left auricular thrombus wa that of Soloff and Zatuchni (FIG 20) [6] Dotter believes that only fairly large thrombi can be visualized with



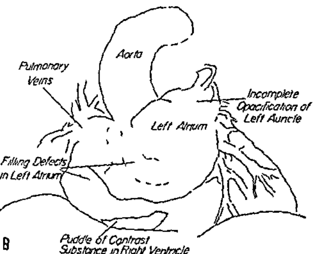


Fig 20 A–B Angiocardiographic demonstration of thrombus in left auricle A 62 year old woman with mitral stenosis auricular fibrillation and cerebral and saddle emboli A Angiogram exposed 14 seconds after injection in frontal and lateral projections Left auricle and aorta well demonstrated Note left auricular filling defects shown in both A and C Residual contrast substance is trapped in the apex of the right ventricle B Tracing of the angiocardiogram

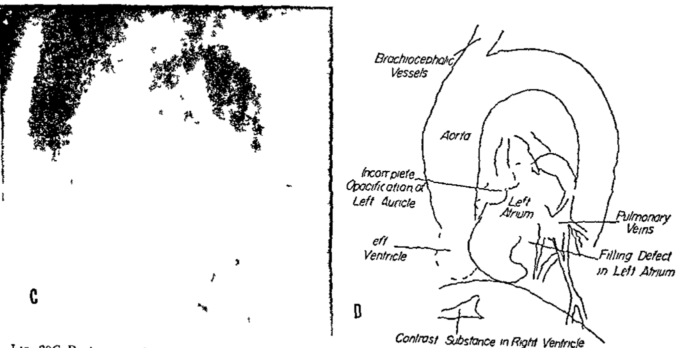


Fig 20C D Angiocardiographic demonstration of thrombus in left auricle C Angiogram Note left auricular filling defects D Tracing of the angiocardiogram (Reproduced by permi ion from Soloff L A and Zatuchni J The angiocardiographic diagno is of left atrial thrombosis Circulation *11* 25 1956)

the present technic In a personal communication he wrote Cardiac movement certainly is an enemy to sharp visualization of small intra cardiac masses Should a mass within the left auricular appendage be large enough to be distinguished clearly from trabeculae carneae or irregularities in the chamber wall angiocardiography would no doubt be of considerable value The value would vary greatly with the technic of the examination The shorter the exposure the more likely the diagnosis for a given sized thrombus The longer the exposure the larger the thrombus which might escape detection With ordinary angiocardiographic technics (1/30 second or longer exposures) the thrombus would probably have to be quarter size or larger to be detected Other factors decreasing detail in the film would have a similar bearing Experimental and preliminary clinical studies indicate that radiographic exposure of 1 millisecond adds significantly to detail and therefore the angiocardiographic yield The technic when perfected may make practical the routine visualization of small intra atrial masses

Angiocardiography has been performed after left auricular catheterization but major complications have occurred in a high proportion [91] There is the probability that before many years angiocardiography may be an important adjunct in evaluating the problem of thromboembolism in rheumatic heart disease Until the technic is perfected clinical acumen in detecting small emboli must remain the best procedure for identifying a left auricular thrombus

Subacute Bacterial Endocarditis after Middle Age

Subacute bacterial endocarditis in the middle aged and elderly occurs more frequently than is generally recognized and often is unsuspected until far advanced In a combined group of 141 patients studied in two hospitals by Anderson and Stafforth [7] and by Wedgwood [1] 69 patients (48 per cent) were over the age of 40 The older the patient the longer the time from the apparent onset to the time of recognition In a study of 76 patients Anderson and Stafforth found the interval was only 3.5 months for patients in the third decade In the seventh decade the time interval was 5.6 months in the eighth decade 10 month

The delay in recognition was ascribed to factors similar to those that delay the diagnosis of rheumatic heart disease in the middle aged first, a paucity of physical signs second the insidious nature of the

disease (two patients had symptoms for two years), and third the failure to consider the diagnosis In five of the 14 patients over the age of 60 studied by Anderson and Staffurth the disease was not recognized until the second admission or after transfer from another hospital

SUMMARY

A high proportion of rheumatic heart disease is unrecognized during life Over one third of patients with rheumatic heart disease die with gross valvular deformities unrecognized Although many die with no outstanding signs or symptoms many seen in middle age are undiagnosed because of an incomplete examination Careful auscultation in the left lateral position and detailed roentgenologic study of the cardiac silhouette and of the mitral valves for significant calcification will identify many questionable cases Major embolism may be the first sign disclosing mitral stenosis In a patient with recognized rheumatic heart disease the probability of embolism should constantly be kept in mind Pulses in the extremities and neck should be charted and periodically rechecked, they should be examined prior to during and immediately after operation, and for 48 hours after operation, in order to detect embolism occurring while the patient is under anesthesia Angiocardiography in certain instances can identify a left auricular thrombu Its status in diagnosis will be clarified in the next few years

The exclusion of rheumatic heart disease makes the diagnosis of arteriosclerotic heart disease with or without hypertension relatively simple Only if rheumatic fever is seriously considered as a cause in every case of supposed degenerative heart disease will all the examinations needed for accurate differential diagnosis be made

8 *Prophylactic Antithrombotic Measures for Systemic Arterial Embolism*

RHEUMATIC FEVER

PROPHYLAXIS against systemic arterial embolism obviously begins with preventing the cause— rheumatic heart disease or at least its progression to a state favoring thromboembolism Going further this means eliminating the streptococcal infections that give rise to rheumatic fever The incidence of the disease may be greatly *reduced* by such measures but complete elimination of it is doubtful because it is impossible to identify and treat every case The usual practice is to *treat only patients* with clinically obvious streptococcal sore throats or those *in whom* throat cultures reveal group A beta hemolytic streptococci *but if these* criteria are too strictly adhered to many rheumatogenic *streptococcal infections* will be missed Streptococci even if present, may not be disclosed except by repeated cultures done with special *technic* Positive results of culture are obtained in only two thirds of *patients even* at the onset of *rheumatic fever* Cluff[4] advocates treating every case of mild *febrile pharyngitis* as a Group A streptococcal infection

Short of this first line defense the only practical *method* of guarding against systemic arterial embolism is the *recognition* and treatment of chronic *rheumatic* heart disease. The first *step* is to estimate the relative risk of embolism *from* the type of lesion and the rhythm but whatever the *estimate* acute *antithrombotic treatment* ordinarily is justified only after the first *recognized* embolism *Hence* the urgency to find evidence of even minor embolism Once the diagnosis *of* embolism is established any *postponement* of antithrombotic treatment assumes that further *embolism will not occur* or that if it does occur it will not be serious. The *reported* experience is overwhelmingly against this assumption on the contrary *recurrence* of embolism is highly probable and as Wright aptly says it usually is *not* the first embolism that kills but one of its successors

Available Antithrombotic Measures

The available antithrombotic measures (TABLE 20) are aimed at reducing one or more of the three factors in thrombosis—damage to endothelium, coagulability of the blood and circulatory stasis They must be selected so as to provide the most effective combination of measures appropriate to each patient s condition

1 Conversion of auricular fibrillation to normal rhythm usually improves cardiac output, thereby reducing congestive failure and stasis Improvement in these conditions will reduce the danger of thrombosis but there is no reason to expect any considerable improvement from the restoration of normal rhythm in the left auricle itself since left auricular contractility is not appreciably improved by the change in rhythm The benefits from conversion are usually temporary in any case since auricular fibrillation eventually returns

TABLE 20—*Site of Effect of Various Antithrombotic Measures in Mitral Stenosis*

Procedure	Damaged endothelium	Coagulability of blood	Stagnation of blood flow
Conversion of auricular fibrillation to normal rhythm	No known effect	No known effect	Improves blood flow
Amputation of appendage	Removes a portion	No effect	Removes stagnation only in appendage
Antithrombotic drug therapy (Dicumarol)	No known effect	Reduces platelet adhesiveness and prothrombin activity	No known effect
Mitral valvoplasty with appendectomy	Removes a portion	No known effect	Corrects causative obstruction

2 Amputation of the left auricular appendage removes only a portion of the damaged endothelium which is the potential site of thrombosis Since the damaged endothelium in the body of the auricle remains and the stagnation continues (because mitral stenosis is still present) further thrombosis is possible Removal of the appendage also interfere

with any subsequent operation on the mitral valve by closing the preferable avenue of approach. As a separate procedure this operation is obsolete. In current practice the choice of treatment is usually made between the two measures yet to be discussed.

3. Antithrombotic drug (Dicumarol) therapy operates through humoral mechanisms by reducing not only prothrombin but also and predominantly its main conversion factor—known as SPCA (serum prothrombin conversion accelerator) or as Factor VII, proconvertin or cothromboplastin.[183] Dicumarol decreases the adhesiveness of the platelets,[9] dilates the vessels,[8] and tends to reduce through fibrinolysis the thrombi already formed.[9] Thus it combats both the original thrombosis and also the propagation of either the primary or the secondary red or fibrin thrombus. After prolonged administration the drug causes deterioration of capillary integrity, but it has no known effect, good or bad, on the damaged auricular endothelium or on auricular blood flow.

Wright and Foley were the first to demonstrate that continuous Dicumarol therapy could diminish the incidence of repeated embolism in rheumatic heart disease. Reports of several series of prolonged application bear out the effectiveness of this treatment (TABLE 21). The frequency of embolism in 98 patients during 1944 months without drug treatment was compared with the frequency during 2995 months of Dicumarol treatment. From the time of the first clinically recognized embolism until Dicumarol was started, an embolus occurred on an average of every seven months; during Dicumarol treatment, however, an embolus occurred only on an average of every seven years. Although the reduction in death or disability from systemic arterial embolism in rheumatic heart disease following the continuous use of Dicumarol necessarily must result from a reduction in either the formation or ejection of left auricular thrombi, the way this is accomplished is not clear. No crucial studies of the incidence of auricular cavitary clots in treated and untreated patients with rheumatic heart disease are yet feasible.

Many single cases of continued freedom from embolism with Dicumarol treatment have been recorded.[1, 3] This freedom depends, of course, on continued therapy. If the drug is discontinued, the patient is again exposed to a high risk of death from subsequent embolism. Such treatment necessarily imposes rigid demands on the physician and the patient. Even with meticulous care either embolism or disquieting

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2. Amputation of the left auricular appendage removes only a portion of the damaged endothelium which is the potential site of thrombosis. Since the damaged endothelium in the body of the auricle remains and the stagnation continues (because mitral stenosis is still present), further thrombosis is possible. Removal of the appendage also interfere

special maneuver for removal of thrombi from the left auricle To prevent cerebral embolism Bailey s group[14] have occluded the innominate and left carotid arteries during the time the auricle was being manipulated Glover Iava O Neill and Janton[9] and others object to this procedure believing it is capable of doing more harm than good This operative precaution moreover still does not protect the rest of the body from embolism which may have serious consequences unless it is recognized early Embolism to peripheral arteries accessible to

TABLE 22—*Recurrence of Embolism after Mitral Valvoplasty*

Author	Patients with systemic arterial embolism before operation	Patient with systemic arterial embolism after operation
Actis Dato and Morino	49	0
Glover et al	84	1 ("Questionable")
Belcher and Somerville	54	4
Bordon	24	0
Bigelow and Greenwood	13	0
Bland Scannell, and Myers	7	1 ("Questionable)
Ellis	139	7
Total	370	13

operative removal must be detected earlier by frequent determinations of the pulses Glover et al[9] reported an incidence of only 6 per cent of surgically produced embolism in patients with definite histories of previous embolism (5 of 84 patients among 452 consecutive valvoplasties) Ellis[68] found the incidence 6 per cent among group III and 20 per cent among group IV *

The reduction of embolism following *recovery from* the operation is

H s clinical classification of patients with mitral stenosis is as follows Group I A benign group without significant symptoms Group II Patients with some functional impairment, usually dyspnea but not progressive Group III, Patients with progressive symptoms *either progressive* dyspnea or repeated attacks of acute dyspnea or pulmonary edema Group IV Cardiac invalids, *most of* whom have chronic congestive failure.

episodes of bleeding may occur It must be admitted that Dicumarol therapy no matter how successful, is only palliative It does nothing to relieve the underlying causes of thromboembolism

4 Combined mitral valvoplasty and left auricular appendectomy corrects the mechanical cause of stasis and also removes an important potential site of thrombosis Theoretically it offers the greatest benefit of any treatment for thromboembolism and furthermore it tends to relieve

TABLE 21—*Systemic Arterial Embolism in Patients with Rheumatic Heart Disease Frequency Before and During Antithrombotic Drug Treatment*

		Before Dicumarol therapy			During Dicumarol therapy		
	Number of patients	Patient months	Number of embolisms	Frequency (months)	Patient months	Number of embolisms	Frequency (months)
Foley Wright McDevitt and Symons	29	765	77	9 9	1346	12	112
Owren	13	386	25	15	295	1	295
Author	14	350	21	16	406	4	101
Beaumont et al	14	168	50	3 3	323	5	64
Cosgriff	28	275	103	2 6	625	13	48
Total	98	1944	276	6 9 Av	2995	35	85 Av

any actual or impending cardiac failure due to stenosis It requires no expensive continuous aftercare (TABLE 22) Of 370 patients with systemic arterial embolism before operation only 13 had embolism after operation The chief danger from operation upon a patient with a history of previous embolism is embolism during operation either in a vital area not amenable to embolectomy (brain) or peripheral embolism amenable to embolectomy but not recognized early enough for a successful operation

With increased experience these dangers have been lessened by appropriate measures in operative technic and by a closer clinical observation Greater care is observed to avoid dislodgement of the thrombus at operation Jamison Rao and Bailey[1 3] have devised a

u ually are not indicated but an attempt to re tore normal rhythm is probably justified If the teno is cau es progressive di ability and if the other criteria for valvopla ty are sati fied the operation hould be done primarily to relieve the increa ing cardiac failure and secondarily as prophylaxis again t possible thrombo i If there is strong rea on to suspect that emboli m is already occurring it may at times be advi able to undertake the recognized ri k of antithrombotic drug therapy

Recognized emboli m is the prime and urgent indication for immedi ate antithrombotic drug therapy in any patient who can safely su tain prothrombin reduction After urviving an attack an untreated patient faces a 45 per cent probability of death from eventual *recurrent embo lism* (FIG 4) The majority of recurrences come in the fir t six month —one third in the fir t month (FIG 5) Whether the original thromb us is extruded en bloc or remains and continues to di charge emboli the underlying factor that cau ed the original formation and mobilization per i t and will continue to cause them This chronic and dangerous *condition mu t be oppo ed* immediately and corrected permanently if po ible

The choice of permanent treatment is by no means clear *Although* surgeons recognize that not all patient are eligible for mitral valvo pla ty and interni ts that antithrombotic drugs are too dangerous for *some patients* there has been no crucial compari on of urgical ver us medical methods to indicate which procedure is preferable after the fir t epi od of emboli m

In an attempt to determine criteria for the *selection of treatment* the hi tories of 14 urvivors of systemic arterial embolism have been reviewed (TABLE 23) All were private patients and their cases were meticulou ly recorded

The natural history of 14 urvivors of systemic arterial emboli m would be expected to be as follow *According to the* evidence about 45 per cent of all deaths should be due to *recurrent* systemic arterial emboli m Furthermore eventual recurrent *emboli m* would be expected in two thirds of the 14 and two thirds of these recurrences should oc ur within a year This did not occur in the 14 udied No deaths were due to emboli m and none of the four recurrences were within a year There were many imilarities *in these ca es* All the patients had long tanding rheumatic heart disea e (mo t of them for over 20 years) with predominant mitral *stenosis* All but two had establi hed auricular fibrillation and of the two with *normal* rhythm one required continuous

nearly complete and the risk of death at that stage is slight (TABLE 22). The general experience of surgeons is in agreement. Although embolisms per patient month before and after operation were not given by Glover, et al.[9] their summary is significant. "The fact can be simply stated that over a postoperative period of approximately six year in an experience of 700 cases of mitral commissurotomy, there has been no instance (with but *one very questionable and minor exception*) of arterial embolism." Harken reported that[108] "in the first 500 patients ... with a 30-month follow-up, there have been but 5 emboli ..." Sir Russell Brock[36] said "... the incidence of embolism after satisfactory mitral valvotomy is very small. In fact I have not had a *single case of embolism occurring after* operation."

The results in a series of cases selected for valvoplasty largely because of repeated embolism are significant. There were no operative deaths in seven cases reported by Bland, Scannell and Myers.[?] Although the seven patients had 30 recognized embolisms in 372 months prior to operation (one every 12 months), there was only one possible small cerebral embolism in the succeeding 70 months after operation.

The risk of death from embolism in a patient with a previous attack who undergoes mitral valvoplasty thus is largely limited to the operation itself. This is about 3 per cent if the patient is in group III and 10 per cent if the patient is in group IV. (About half of those with operative embolism die.) If the patient is not operated upon and not given continuous antithrombotic drug treatment, the risk of death from eventual embolism is about 45 per cent.

Choice of Antithrombotic Procedure

Since the risk of death and disability from systemic arterial embolism varies according to the rhythm, the type of mitral valve lesion, and the history of previous embolism (TABLE 13), the treatment must be selected by weighing the dangers against the benefits to be expected.

In normal rhythm with no progressive disability, the mortality from embolism is less than five per cent (TABLE 12). Since no therapy could be expected to improve this rate, the patient in this situation should merely be watched for signs of embolism.

In auricular fibrillation with no recognized embolism, the mere presence of the arrhythmia increases the risk of death to about 10 per cent. If the mitral valve is purely stenotic, the risk is nearly doubled (TABLE 12). If no embolism has been detected, antithrombotic measures

quinidine therapy Attempts to maintain normal rhythm by quinidine therapy were succes ful for some months or years in a few cases but only in Ca e 2 was normal rhythm permanently maintained Seven had recognized embolism before conge tive heart failure was clinically apparent Dicumarol therapy was instituted in every case when embo li m was recognized and had been maintained for a total of 406 patient months at the time this study was made Dicumarol was discontinued in only one case becau e of headache and Tromexan was sub tituted with success It never became necessary to discontinue treatment because of hemorrhage in any patient During therapy there had been four recognized embolic episodes and none were fatal Seven patients died of conge tive failure

In even of the 14 cases mitral valvoplasty was contraindicated but continuous Dicumarol therapy was chosen as preferable to expectant treatment. All the patients had far advanced disease and six were in congestive failure Their average age at the time of the first recognized embolism was 55 years and death within a few years from congestive failure was apparently inevitable Six died of this cau e an average of three and one half years later During 126 months of continuous antithrombotic therapy there were two recognized emboli ms—far less than the expected frequency—followed by recovery Although the treatment had no measurable effect on congestive heart failure it may have prevented death from emboli m.

The other seven patients also receiving antithrombotic drug therapy were eligible for operation by all criteria except age and progressive disability Four were aged 30 to 45 year the others 53 to 56 years Glover Janton and O Neill[93] among other it should be noted do not accept age per se as a contraindication to operation Congestive failure and progressive disability were present in only one of the even at the fir t embolism and this was corrected and controlled (Case 8) Con gestive failures in this case however returned and the patient died five years later Two other patients subsequently developed progres ive disability (Ca es 9 and 10)

A case worth reporting in detail follows

Case 9—Mrs D F age 41 was first seen on August 6 1951 In 1926 at the age of 16 rheumatic heart disease was fir t diagnosed In 1949 at the age of 39 she first noticed "her heart wasn t beating right This apparently was the on et of auricular fibrillation 23 years after the recog nition of rheumatic heart disease There was no restriction of activity She

TABLE 23—*Results in 14 Patients with Systemic Arterial Embolism Receiving Dicumarol*

Ca e	Sex	Age	Status at fir t recognized emboli m conditions associated with mitral stenosis	Emboli preceding therapy	Dicumarol therapy (mos)	Emboli during therapy	Duration of disease (yrs) RHD	AF	Present status Remarks	Age now
1	F	46	Auricular fibrillation congestive failure marked aortic regurgitation	1+	9	0	29	?	Died of congestive failure	53
2	M	39	Normal sinus rhythm (with quinidine) congestive failure aortic regurgitation	1+	40	1 cereb no resid	?	NSR	Died of congestive failure	48
3	F	55	Auricular fibrillation uncontrolled conge tive failure	1+	25	0	26	10+	Died of congestive failure	57
4	M	52	Auricular fibrillation uncontrolled congestive failure	2+	6	0	40	3	Died of congestive failure	53
5	F	64	Auricular fibrillation uncontrolled congestive failure	1	6	0	40	?	Congestive failure persists Still ineligible for operation	64
6	F	65	Auricular fibrillation uncontrolled congestive failure	1+	23	Minor cereb	40	?	Congestive failure persists Still ineligible for operation	67
7	M	64	Normal sinus rhythm	1	17	0	?	NSR	No congestive failure Still ineligible for operation	65
			Total		126					
8	M	45	Auricular fibrillation	1	60	0	?	12+	Died of congestive failure	50
9	F	41	Auricular fibrillation	3	34	0	25	4	Mitral valvoplasty when progres ive disability developed	43
10	F	56	Auricular fibrillation	1+	13	0	?	12+	Progressive disability	62
11	M	53	Auricular fibrillation	5+	96	1 prob after 5 yrs	?	9	Functional Class II	66
12	F	53	Auricular fibrillation	2	41	1 after 3 yrs	?	1+	Functional Class II	58
13	M	30	Auricular fibrillation	2	23	0	?	4+	Lost to follow up	32
14	M	41	Auricular fibrillation	3	10	0	26	1	Lost to follow up	46
			Total		280					

probably the cause of them. During the pa t two year the patient has suffered s veral tran itory episodes of unconsciou ness and numbness un bn and weakne s of the right arm, interprete l as minor cerel ral emboli m Tromexan therapy has been in tituted with no headaches resulting and no further emboli m However the patient has increa ing ly pnea on eff rt and the ri k of urgery is greater at her present age 62 years

In 200 months of continuous Dicumarol therapy of the seven patient eligible for valvopla ty there were only two embolic episodes an average of one every 11 year Even for the two patients (Cases 11 and 12) with treatment totaling over 11 year the frequency of emboli m is much lower than it was before treatment and progre ive di ability has not occurred de pite the unfavorable prognosi u ually a ociated with emboli m and fibrillation

Cas 11—A 53 year old man wa di able l with *monoplegia* by the fir emboli m (cerebral) During the next five years he ha l repeate l emboli m to the spleen mesentery and kidneys which require l hi h spitalization From the a e of 58 (January 1948) he was treated c ntinuou ly wit Dicumarol and had no further clinical emboli for seven years I e enth there was ome evidence of a mesenteric emboli m which left n noticeabl equela He has taken Dicumarol continuously f r over ei ht year

Case 12—A 5 year old woman was first seen after having had tw mbolism (one cerebral) in the previous two years After 37 m nths Dicumarol therapy another cerebral emboli m occurred

It is debatable whether the seven patients eligible for mitral valv pla ty would have fared better had operation been perf rmed earl but in retro pect it seems that they would have Although progres i di ability was not pre ent at fir t it developed later in three patien (Cases 8–10) One of these patient died (Case 8) another has und gone succes ful valvoplasty (Ca e 9) and the third is now over 60 a refuses to con id r an operation (Case 10) While no ignificant d ability has occurred in cases 11 and 12 after years of Dicumarol therap till thi cour e has required vigilance has been expen ive for the p tient and ha been overca t by the con tant po ibilities of patholo bleeding and of further embolism

Th c ndition of the patient in case 11 at age 66 is amazing He n progres ive dy pnea is able to walk without difficulty and has ympt ms of beginning cardiac failure It is highly indicative of l n life po ible in certain patients with rheumatic heart di ease no emboli m occurs Embolism has occurred once each in cases 11

said she was able to run up tairs without shortness of breath In March 1950 she developed pain in the leg which was diagno ed as an arterial embolus She was hospitalized for two weeks In April of 1950 she had lower abdominal pain anorexia and vomiting which were interpreted a me enteric arterial embolism Following this epi ode she still suffered no limitation of phy ical activity In August 1951 following pain in the left upper quadrant a palpable spleen was noted Dicumarol was then given and the treatment maintained for 29 months with no recurrence of emboli m A dosage of 37 5 mg of Dicumarol daily maintained the prothrombin activity between 15 and 35 per cent In the last six months of 1953 sign of increasing di ability appeared She noticed shortness of breath and easy fatigability which had not been present prior to then

Examination of the heart had always indicated predominating mitral stenosis A low pitched diastolic murmur was heard at the apex with no evidence of mitral regurgitation The roentgenogram of her che t revealed a moderate accentuation of vascular markings suggestive of minimal pas ive congestion The cardiac silhouette showed a rather marked prominence of the pulmonary conus area The right anterior oblique view showed moderate prominence in the area of the left auricle The finding therefore were those of apparently pure mitral tenosis with evidence of left auricular enlargement left auricular failure and symptoms of undue dyspnea and easy fatigability She apparently was a sati factory candidate for mitral valvo plasty *Dicumarol was discontinued for two weeks before operation* She was operated upon on January 14 1954 by Dr John C Jones

Operative Note The pulmonary artery was large and ten e The auricular appendage was small and contracted It contained both friable and black clot in addition to organized carred old clot and the opening into the auricle was extremely small The body of the auricle was large and no clot was felt therein The anterior valve leaflet was calcified with a plaque of calcium about 1/4 inch thick The opening in the mitral valve itself was less than 1 cm in diameter There was no regurgitation either before or after finger fracture The remaining opening at the end of the operation was between 3/4 inch and 1 inch long

Since the operation the patient has had no evidence of further embolism and has been changed from a functional classification III into cla s II The auricular fibrillation was reverted by quinidine but the dose required for maintenance was infea ible and auricular fibrilla tion was accepted as an establi hed rhythm

Another case worth reporting is that of a woman who had a minor cerebral emboli m at the age of 56

Case 10—The patient was given continuous Dicumarol therapy for six months but persistent headaches developed apparently an exacerbation of a migraine tendency that had appeared earlier in her life Since the headaches did not recur after discontinuance of Dicumarol this drug was

auricular fibrillation survive to normal expectancy with only minimal disability if the thromboembolic mechanism does not occur

ARTERIOSCLEROTIC HEART DISEASE

It would be unwise to exclude the future possibility of operative removal of necrotic myocardial areas predisposing to thrombosis. The excision of ventricular aneurysms in selected cases already has been achieved.[14] The indications for such procedures and the necessary perfections of technic must be relegated to the future. Increasing experience in the use of antithrombotic drugs in arteriosclerotic heart disease, however, is readily crystallizing opinion regarding indications for their use.

Whereas the use of Dicumarol in rheumatic heart disease seems justified only to prevent the recurrence of embolism after it has already been recognized, it is indicated in arteriosclerotic heart disease as soon as those conditions occur which most often give rise to a primary thrombus. The danger of thrombosis in rheumatic heart disease cannot be similarly limited to a short period; in arteriosclerotic heart disease it is greatest *immediately* following myocardial infarction and in any period of congestive heart failure.

Effect of Dicumarol on Formation of Ventricular Mural Thrombi

In several necropsy series the effect of Dicumarol on formation of ventricular mural thrombi has been compared with findings in untreated patients. These studies reflect the results obtained in practice and reveal a wide variety of conflicting conclusions.

First, that the significant effect of Dicumarol is in opposing the mobilization rather than the formation of thrombi. Burchell[38] quoting results he obtained with McQuay and Edwards (unpublished data) found as many mural thrombi following myocardial infarction in patients who had been treated with Dicumarol as in those who had not, but of the 16 treated patients with mural thrombi none had gross systemic emboli at necropsy. At the same clinic in 35 per cent of 83 untreated cases of acute myocardial infarction with left sided mural thrombi, evidence of systemic arterial occlusion was found at necropsy.[374]

Second, that the effect is rather in inhibiting clot formation, the reduction achieved is about 50 per cent. Howell and Kyser[119] contrasted the findings in 34 patients dying of myocardial infarction and receiving

12 and in addition these patients face the inevitable consequences of congestive heart failure at which time the opportunity for successful operation will have passed

It would appear then *that mitral valvoplasty cannot be ruled out of* consideration merely because of the added risk imposed by old age or because the absence of progressive disability makes the operation less urgent These 14 cases illustrate the individualization necessary in determining proper treatment A tentative program based on the available evidence is as follows Patients with rheumatic heart disease and auricular fibrillation are regarded as the most likely (four to one) to have systemic arterial embolism When angiocardiographic technic for visualization of thrombi is improved these patients will be the ones to be considered for study by that method

The recognition of systemic arterial embolism is considered to demand that immediate Dicumarol prophylaxis against recurrence (unless contraindicated) be continued until the most suitable future treatment can be selected Mitral valvoplasty is preferred to lifelong antithrombotic drug therapy, and progessive disability is not considered an indispensable criterion Embolism alone is an adequate reason for operation For the patient eligible for valvoplasty, drug therapy not only is onerous and expensive but merely postpones the time when operation will be necessary When that time comes the patient s age will have increased the risk of operation perhaps so far as to make it unjustifiable The danger of death or disability from subsequent embolism must be measured against the danger of operative death or of disability from an embolus during operation The mortality from eventual recurrent embolism can be estimated at 45 per cent whereas the mortality at operation is now about five per cent Ellis[68] has shown that the risk of an embolus during operation on a patient with previous embolism in Group III is only five per cent but in Group IV 20 per cent This is an added reason for early operation However if operation is contraindicated drug therapy should be continued for life provided the necessary conditions can be reasonably assured If fibrillation is present an attempt should be made to change the rhythm to normal and maintain it. Only when circumstances forbid either operation or continuous drug therapy should expectant treatment be resorted to

If systemic arterial embolism has not occurred in rheumatic mitral stenosis it is justifiable to await the progression of disability before recommending operation Many patients with cardiac enlargement and

thrombi in 63 per cent of 133 patients without anticoagulant treatment who survived more than three days and in 78 per cent of 23 patients who were given anticoagulant drugs more than three days after the onset Among 51 patients to whom anticoagulants were given prior to the third day however only 15 per cent had mural thrombi—a significant reduction—emphasizing the need to begin Dicumarol prophylaxis within three days of the onset of myocardial infarction

It is apparent that in myocardial infarction Dicumarol as given clinically prevents the formation of ventricular thrombi in only 50 per cent of patients at best Either the usual prothrombin reduction is not sufficient to prevent formation of thrombi in half of the patients or an adequate level is not continuously maintained McQuay Burchell and Edwards[1 1] believed they had maintained the accepted effective prothrombin reduction in all but 10 per cent of their patients and Howell and Kyser[119] reported mural thrombi in four of 15 patients whose prothrombin activity had been maintained between 20 and 30 per cent

Although none of these studies separated the good risk from bad risk cases there can be little doubt that the probability of left ventricular thrombosis is much greater in patients with large transmural infarcts and congestive failure

In assessing the value of Dicumarol however it is necessary to consider not merely its lifesaving value or its inhibition of mural thrombosis but also its total antithrombotic effect and in addition other possibly valuable properties not related to prothrombin reduction

Prophylactic Use of Dicumarol in Acute Myocardial Infarction

The efficacy of Dicumarol in reducing mortality and thromboembolism in properly selected cases of acute myocardial infarction is generally accepted At the International Conference on Thrombosis and Embolism at Basel in 1954 the opinion was unanimous that anticoagulant drugs should be given to every patient with acute myocardial infarction unless there were contraindication

This view is opposed however by Russek et al[13, 16] who would limit Dicumarol prophylaxis to about 30 per cent of all cases by excluding mild or good risk cases from treatment They base their dissent on their estimate of the risk of Dicumarol therapy (which they consider excessive in comparison to the danger of mild myocardial infarction) and on a contention that these milder cases can be reliably identified

Dicumarol with those in 98 untreated patients. The frequency of mural thrombi in those *receiving prophylactic treatment* was 30 *per cent*; in the untreated 54 per cent. These authors considered the control of thrombosis, as determined by prothrombin activity, to be good in 15 patients, fair in 9, and poor in 10. Surprisingly there was little difference between these treated groups (good, fair and poor) in the *actual incidence of mural thrombi but the difference between the treated* and the untreated according to chi square analysis was statistically significant. In another series of 121 patients dying of acute coronary arterial occlusion without antithrombotic drug treatment, Kissane, Fidler and Conn[131] found mural thrombi in 48 per cent, while among 191 receiving antithrombotic drugs they found mural thrombi in only 26 per cent. Although these authors did not correlate the incidence of mural thrombi with the degree of reduction of prothrombin activity, they concluded that the incidence was significantly reduced by the drug. In a similar study, Wright, Marple and Beck[6] found mural thrombi in 63 per cent of 18 untreated patients but in only 32 per cent of 41 who had received Dicumarol. Among 75 untreated patients Glueck, Ryder and Wasserman[96] found 41 per cent with mural thrombi as against 23 per cent of 56 adequately treated patients (adequate range was 30 per cent or less).

Third, that in fatal myocardial infarction the drug does not cause a significant reduction in the incidence of ventricular cavitary thrombi or of peripheral infarction (presumptive evidence of embolic occlusion). Gilchrist and Tulloch[58] found that of 139 untreated patients 56 (40 per cent) who died later than 24 hours after the attack of myocardial infarction had ventricular mural thrombi. Of 80 treated patients dying more than 24 hours after the attack 29 (33 per cent) had ventricular mural thrombi. The incidence of peripheral infarction in the untreated patients was 21 per cent and among the treated was 15 per cent. These figures in regard both to thrombosis and to peripheral infarction were considered suggestive but not statistically significant. These authors did find however a pronounced and highly significant reduction in the incidence of pulmonary infarction in the treated but fatal cases — 3.4 per cent (3) in 88 treated cases and 17 per cent (27) in 160 control autopsies.

Fourth, that the drug does not cause a significant reduction of ventricular mural thrombi unless given within three days after the clinical onset of myocardial infarction. Lee and O'Neal[149] demonstrated mural

will fail to bring out that high incidence of thromboembolism which can be detected by active search according to previously defined criteria

In another controlled study Furman et al[81] found no significant difference either in mortality or in thromboembolism between 50 Dicumarol treated and 76 untreated good risk patients Burton[41] however did find such a difference in 156 good risk patients receiving Dicumarol of whom 2 per cent died and 6 per cent had thromboembolism in contrast to 5 per cent mortality and 11 5 per cent incidence of thromboembolism among 58 control patients As Gilchrist and Tulloch[83] observe If it can be verified that 3 in 100 good risk patients can in fact be saved who would otherwise be expected to die and the incidence of thrombotic complications halved thanks to the use of these drugs then anticoagulants would appear justified so far as the family and the individual wage earner are concerned

The late result of continuous Dicumarol prophylaxis for mild cases have not been well established Suzman Ruskin and Goldberg [4] found no reduction in late mortality among 15 surviving good risk patients receiving Dicumarol up to 76 months after the onset of acute myocardial infarction but Keyes Drake and Janney Smith[139] though they did not separate their good risk patients did note a profound reduction in mortality four years after the attack in 71 patients with a single infarct who received Dicumarol, with a mortality rate of 8 per cent against a rate of 41 per cent in 186 comparable untreated control patients

Danger of Dicumarol Therapy in Myocardial Infarction

Russek [10] bases his contention that the drug is more dangerous than the disease upon Wright s estimate that Dicumarol therapy contributes to the death of 1 7 per cent of patients so treated But while Russek maintains (in the face of considerable disagreement) that it is possible to distinguish reliably between good risk and bad risk cases soon after onset, he applies this estimated death rate to the good risk cases although it was derived from a study of myocardial infarction in all degrees of severity It cannot reasonably be expected that fatal complications due to Dicumarol would be as frequent in mild or good risk cases as in severe cases with a high risk

Wright Marple and Beck [76] made a controlled study of such good risk cases (adhering to Russek s criteria) in which they found 14 instances of bleeding in 114 Dicumarol treated patients and none in

soon after onset Russek[209] concludes that the use of the drug in "good risk cases is costly, burdensome, and unnecessary Schnur[16] too objects to the expense inconvenience, and danger of Dicumarol prophylaxis as well as a universal difficulty in maintaining constantly effective concentration in the blood In mild cases he contends only one death in one hundred is theoretically preventable by Dicumarol prophylaxis One life in one hundred of course, is well worth saving and the effort should be made unless it can be demonstrated that the drug is more dangerous than the disease

Value of Dicumarol in Good Risk Cases

Since the value of Dicumarol in more severe cases of myocardial infarction is generally admitted attention can be turned on the controversial good risk case Russek considers good risk patients as those without (1) a history of previous myocardial infarction (2) intractable pain, (3) extreme degree or persistence of shock (4) significant enlargement of the heart (5) gallop rhythm (6) congestive heart *failure (7) auricular fibrillation or flutter ventricular tachycardia* or intraventricular block and (8) diabetic acidosis or other states predisposing to thrombosis

The immediate mortality rate in untreated mild cases is so low that neither beneficial nor detrimental effects of Dicumarol can be demonstrated without a careful study of a large series Since a double blind test is not feasible,[94] the best available method is to treat alternate good risk patients and compare the mortality rate and the thromboembolic complications with those for the untreated good risk patients This has been done by the American Heart Association s Committee on Anticoagulants Wright Marple and Beck[6] reporting for this committee found no significant difference between the immediate mortality rates for 114 Dicumarol treated patients (1 8 per cent) and for 65 control patients (1 5 per cent) On the other hand they found thromboembolic complications in more than 20 per cent of untreated patients, against nine per cent in those treated They emphasize that prevention of death is not the only objective of treatment and that a reasonable risk may be taken to prevent such nonfatal complications as cerebral and peripheral arterial embolism pulmonary embolism and recurrent infarction They note, too that Russek found thromboembolic complications in only three per cent of untreated good risk cases but they feel that a retrospective study like his limited to reviewing hospital record

can be maintained safely in patients having mild attacks it is highly desirable The number of patients having mild attacks (without treatment) who develop serious thromboembolic episodes is a convincing bit of evidence favoring treatment The dangers of bleeding are overemphasized Bleeding complications which occurred in supposedly skilled hands over five years ago when physicians had less experience would not occur today

When contraindications to the use of Dicumarol are listed the emphasis is usually placed on the presence of lesions that might predispose to bleeding but this is not the most important contraindication Probably more important is the inexperience of the physician and next the lack of reliable laboratory control

Rusk's insistence that consideration should be given to the probable results of therapy administered in smaller hospitals or in the patients homes under the guidance of less skilled hands is well taken The proper administration of Dicumarol with safety requires a highly skilled technic It is not to be undertaken by an unskilled physician in either a small or large hospital with questionable laboratory facilities nor usually to be started in the home The admitted inadvisability of using the drug under such undesirable circumstances however can in no way negate the advisability of the use of the drug under proper condition The use of any procedure requiring special equipment is indicated only under suitable conditions The recommendation of the Committee on Anticoagulants of the American Heart Association in its initial report in 1948 still seems justified Anticoagulant therapy should be used in all cases of coronary thrombosis with myocardial infarction unless a definite contraindication exists

CONGESTIVE HEART FAILURE

If Dicumarol can be given safely as the evidence suggests it should be administered for congestive heart failure Significant reduction in thromboembolism has been recorded in treated patients and contrasted to untreated control patients by a number of investigators[5, 68, 110] Griffith et al[3] found improvement in all types of heart disease save cor pulmonale and luetic heart disease

Congestive heart failure contributes to the formation of peripheral venous thrombosis and pulmonary embolism in rheumatic heart disease and to the formation of left ventricular thrombi in arteriosclerotic heart

the 65 untreated control patient. Of the 14 instances of bleeding, however, only one was severe and was due, they believed, to "obvious careless management." The patient's prothrombin time had been 56 seconds or longer for a week, and over 60 seconds for three days; he was then given another 110 mg. of Dicumarol. There was no contraindication to the use of the drug except the most important contraindication of all—the incompetence of the attending physician. Nevertheless the patient recovered from the hemorrhage.

The prevailing picture of Dicumarol therapy for acute myocardial infarction is far removed from such mishap. With increasing experience the incidence of death from hemorrhage is steadily decreasing, especially in good risk cases in competent hands.

Regarding acute myocardial infarction specifically, a compilation of 15 series, covering 1572 treated cases, indicates severe bleeding in 0.7 per cent (11 patients) with hemorrhage contributing to death in 0.3 per cent.[6] Burchell[9] points out that in low risk cases the dangers of anticoagulant therapy are minimal, control is most readily achieved and the possibility of salvage is greatest. "We are willing to give anticoagulant therapy to one hundred or more patients with the hope of preventing one death," he declares.

It can be concluded, then, that just as the greater risk of hemorrhagic death is worth taking in severe myocardial infarction, so the slighter risk is justified in mild, good risk cases. In a good risk case, if the prognosis is eventually found to be correct, the patient will have been protected both against fatal accident and also against serious (though *nonfatal) thromboembolism. De Francisco and Wright have reported* 14 instances of either serious or fatal thromboembolism in 14 initially mild cases. If, on the other hand, the infarction is more severe than first believed (Halpern, Lemberg, Belle and Eichert[107] found it necessary to revise their evaluation *in one third of 107 cases),* the patient will have had the benefit of Dicumarol therapy during the crucial first three days, when it is most effective. If Dicumarol therapy is denied in supposedly good risk cases, it will be denied also in those cases where the disease originally seems to be less severe than it really is.

Program of Treatment for Good Risk Patients

In the absence of conclusive evidence (which cannot well be forthcoming since double blind tests are infeasible) the wise physician *must depend on general principles. If reduced coagulability of the blood*

9 Continuous Antithrombotic Drug Therapy in Heart Disease

ARTERIAL EMBOLIZATION in patients with rheumatic heart disease and recurrent myocardial infarction both are becoming accepted by many physicians as reasonable indications for continuous antithrombotic drug treatment. Further experience suggests that patients with severe first attacks of myocardial infarction can be benefited by long term treatment.[135] Chronic congestive heart failure is another probable indication although Friedberg[60] admits that "the difficulty of convincing many physicians of their [anticoagulants'] value in myocardial infarction despite impressive statistical evidence in their favor suggests that it will be even more difficult to obtain convincing evidence of their benefit in heart failure."

The ability of Dicumarol to reduce prothrombin activity and inhibit intravascular coagulability is undisputed. In an era when so many deaths are caused by clots forming in blood vessels during life, the availability of a drug which can diminish this tendency to thrombosis is a clinical god end. If safe, a continuing reduction in coagulability would be desirable in every person in whom the dangers of potential thrombosis are continuously present.

Experience continues to demonstrate that such prolonged therapy if properly controlled is as safe as short term therapy. It is feasible, compatible with an active life and with travel, and requires only reasonable precaution. This attitude marks a dynamic turning point in the management of previously discouraging thromboembolic disease, or as Tulloch and Wright[1] state, a change "from a static and resigned approach in which patient and physician alike awaited with apprehension the possibility of a series of serious or even fatal developments." In no other cardiovascular disorder is Dicumarol so effective as in the reduction of recurrent embolism in rheumatic mitral stenosis. Although its chief mode of action is not known—whether it prevents the formation, propagation or mobilization of left auricular thrombi—there should be little doubt that the desired end result, the prevention of recurrent systemic arterial embolism, is achieved.

disease It increases the incidence of thrombosis in diseased arteries in both diseases Jordan, et al [13] demonstrated the increased incidence of left ventricular thrombi in arteriosclerotic heart disease associated with congestive failure

Prophylactic Dicumarol treatment is indicated for congestive heart failure resulting from degenerative heart disease from any cause

SUMMARY

Three measures are available to reduce the recurrence of left auricular thrombosis in rheumatic heart disease drug (Dicumarol) therapy to lower the coagulability of the blood as far as the danger of hemorrhage will permit combined mitral valvoplasty and left auricular appendectomy to correct the mechanical cause of stasis and to remove an important potential site of thrombosis (auricular appendectomy is no longer done as an isolated procedure) and conversion of auricular fibrillation to normal rhythm to improve cardiac output and diminish stasis

Upon recognition of systemic arterial embolism Dicumarol prophylaxis should begin immediately unless positively contraindicated Patients eligible for mitral valvoplasty may well submit to operation even before progressive disability makes the operation more urgent and the condition less favorable If operation is contraindicated or refused life time antithrombotic drug therapy should be maintained if feasible If the auricle is fibrillating normal rhythm should be restored and maintained if possible

It is generally accepted that the risk of hemorrhage in severe acute myocardial infarction is well justified by the salvage obtained with prompt and adequate Dicumarol prophylaxis directed toward preventing thrombosis both in the left ventricle and in peripheral vessels In milder cases however the less demonstrable benefit of Dicumarol still justifies the slighter risk and insures against the graver risk in those cases (perhaps as many as one third) where the disease unpredictably becomes worse

Dicumarol is indicated on the appearance of congestive failure either in rheumatic heart disease in which this complication predominantly increases the tendency toward venous thrombosis or in arteriosclerotic heart disease in which in addition it promotes left ventricular and arterial thrombosis

had died (FIG 21) In the mild cases the authors found no significant reduction to justify continuing therapy beyond the acute phase

Keyes Drake and Janney Smith[239] gave Dicumarol continuously to one group of patients who had single infarcts and continuing anginal symptoms and to another group with multiple infarct Comparing the result in those groups with results in two similar groups who had received no Dicumarol during or after the attack they found that four years after the single infarction 41 per cent of the untreated patients were dead but only 9 per cent of the Dicumarol treated had died Among those with recurrent infarction 63 per cent of the untreated died within four years of the first attack compared to only 12 per cent of the Dicumarol treated patients These findings suggest that *even* after an initially mild attack the patient with continuing anginal symptoms will benefit from long term therapy

FACTORS AFFECTING DICUMAROL THERAPY

Successful continuous treatment with Dicumarol hinges on the reliability of the patient the physician and the laboratory Physicians experienced with this drug learn to apply strict criteria in *determining* the eligibility of all three parties but many others without such experience simply shun the drug entirely because of an unwarranted fear of inducing hemorrhage The danger of bleeding varies with the condition treated Pathologic hemorrhage is less frequent in rheumatic heart disease than in *other* thrombotic conditions— first because the younger patients usually have fewer potential sites of serious bleeding and second because it is not necessary *to greatly* reduce prothrombin activity in order to control the thromboembolic tendency *In addition* there is the reassurance in every case of reduced prothrombin *activity* *that the* vitamin K_1 preparations can rapidly restore normal coagulability *These factors assure greater* safety in using Dicumarol permit its application to a larger number of patients and justify a *longer* interval between laboratory tests

Beyond this simple outline there are inevitable complications which unless understood will cause the *therapy to* be condemned Many physicians are still puzzled by the fact that within the same supposedly protective range of prothrombin activity *thromboembolism* may occur at one time and hemorrhage at another

However most vascular diseases present the same dilemma—*the*

Selected patients who survive acute myocardial infarction live longer and have fewer recurrences with continuous Dicumarol therapy. Three causes of death await two thirds of the survivors of acute myocardial infarction, according to Achor et al.[1] These are congestive heart failure, recurrent myocardial infarction, and sudden death without congestive failure or acute infarction. In 21 (8 per cent) of 250 patients systemic

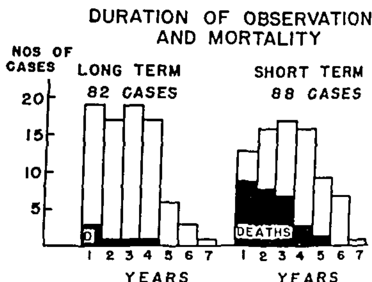


FIG 21 Mortality rate among patients with myocardial infarction given Dicumarol only during acute attack and those given it continuously. (By permission from Suzman, M. M., Ruskin, H. D., and Goldberg, B.: An evaluation of the effect of continuous long term anticoagulant therapy on the prognosis of myocardial infarction. A report of 82 cases. Circulation *12* 338, 1955.)

arterial occlusion (thrombotic or embolic) was a major cause of death. Dicumarol could be expected to be beneficial in congestive heart failure and to reduce the incidence of recurrent infarction and systemic arterial occlusion. The antithrombotic action plus the presumed vasodilatory effect could reduce the incidence of sudden death.

Suzman et al.[74] have compared the mortality rate in two groups of patients surviving acute myocardial infarction. One group of 88 received Dicumarol only during the acute phase, the other 82 received it both in the acute phase and continuously thereafter (FIG 21). Before the end of the fourth year, 27 (33 per cent) of those on short term therapy were dead but only six (7 per cent) of those on long term therapy

against thromboembolism and bleeding Either complication or both of them together may occur in certain instances

Tulloch and Wright [1] reported thromboembolism occurring during Dicumarol therapy in 13 patients whose prothrombin time indicated a supposedly adequate range (25 to 40 second 20 and 10 per cent of normal) and even in three patients whose prothrombin time was longer than 40 seconds (below 10 per cent) In all cases of bleeding studied by Barker [16] prothrombin activity was in the so called therapeutic range (10 to 30 per cent) Foley Wright McDevitt and Symons [77] report instances of bleeding in 85 patients receiving long term antithrombotic drug therapy for various conditions in which the prothrombin time was within therapeutic range in seven and further investigation in these cases revealed pathologic conditions e g hemorrhoids gynecological disorder and renal calculi In four similar cases studied by Owren [164] the causes of bleeding were renal calculus renal tuberculosis bronchiectasis and gastric ulcer Unsuspected carcinomas of the bowel or the uterus and ulcers of the bladder and the duodenum have been disclosed by bleeding occurring at ordinarily desirable levels of prothrombin activity [74] These findings indicate that the lesion and not the prothrombin level determines the onset of *hemorrhage* The level at which bleeding is induced in this lesion determines the *safe level* Since it is impossible to detect much less evaluate every potentially hemorrhagic lesion in the body the risk cannot be measured except statistically The supposed therapeutic range can only be a compromise low enough to prevent clotting and high enough to prevent bleeding in most instances If prothrombin activity *were further reduced* thrombosis would be less probable but the danger of bleeding would become prohibitive If the reduction were lighter bleeding would be less of a danger but the risk of thrombosis would be greater

Danger of Bleeding (Minor and Major)

Minor bleeding of a degree neither fatal nor disabling frequently occurs with prothrombin activity in the therapeutic range At accessible sites as in epistaxis *oozing* from the gums or areas of purpura it can ordinarily be ignored (if blood dyscrasias are *excluded*) since it does not reflect the presence of potential bleeding lesions elsewhere nor augur future serious bleeding Such bleeding probably results from a localized capillary defect and any risk it carries is far outweighed by the risk of disability or death from thromboembolic complications

danger of thrombosis from damage to the intima at one site, and of bleeding from a break through the adventitia at another. Correspondingly, there are not one but two important levels of prothrombin reduction: the *effective level* at which thromboembolism is prevented and the *safe level*, below which serious bleeding may occur. Neither of these levels is predictable in any one patient.

The effective level varies with the type and particular stage of vascular damage. In Buerger's disease and "blue phlebitis" (phlegmasia cerulea dolens), for example, the risk of thrombosis is high;[3-5] in acute rheumatic arteritis and auriculitis it is low; with normal cardiovascular endothelium thrombosis cannot occur.

While prothrombin activity in Buerger's disease might have to be reduced to 10 per cent of normal or lower to prevent thrombosis, in rheumatic arteritis a moderate reduction to 50 per cent might possibly be sufficient to prevent thrombosis. In the acutely necrotic stage of myocardial infarction, the tendency for cavitary thrombosis is great and a reduction below 20 per cent initially might be necessary; however, as the endocardium heals, the thrombotic tendency lessens until, if complete healing takes place and normal endothelium covers the area, no thrombosis will occur at that site even with normal prothrombin activity.

The safe level is individually determined but cannot be individually predicted. It depends on the nature and state of the vessel wall of the whole vascular tree. In the normal blood vessel there is no tendency toward either bleeding or thrombosis. Quick[19] assures us that when the vascular system is intact there will be no hemorrhage even when the blood is incoagulable from any cause: lack of thromboplastinogen (as in hemophilia), prothrombin deficiency, heparinization or total absence of fibrinogen. "Hemorrhage occurs," he states, "only when an *additional factor* is superimposed on the original coagulation defect." (Italics are mine.) Similarly, no bleeding occurs with the coagulation defect produced in man by Dicumarol if the vessel walls are intact.

Clinically, bleeding occurs because of these additional factors. Lesions such as a peptic ulcer or a cerebral aneurysm, although not bleeding with a normal prothrombin activity, will begin at possibly an 80 per cent or 50 per cent level, or possibly only if the activity is reduced below 10 per cent. To be safe, prothrombin levels must stay above these figures, an impossibility in all cases since these figures are unpredictable. Any arbitrary range of prothrombin values cannot always protect

cardial infarction concluding "A little anticoagulant protection is definitely better than none"

Griffith et al[10] found that among patients with congestive heart failure whose prothrombin activity was maintained below 60 per cent only 1.8 per cent had thromboembolism (all types) while among those with lighter reduction the frequency was 15 per cent. These authors suggested 45 per cent of normal as the safe prophylactic maximum. Brambel, Hunter and Fitzpatrick[33] also believe that between 45 and 50 per cent is a protective reduction. Burt[40] stated that her aim was to keep the prothrombin level between 30 and 60 per cent.

With regard to chronic rheumatic heart disease there is no controlled study to show that the formation of left auricular thrombi is prevented. The only practical control in evaluation of this therapy is the patient's previous history compared with his course following *treatment* (TABLE 21). The evidence so obtained that Dicumarol does reduce the incidence of embolism by only a moderate reduction of prothrombin activity is convincing. Regulating therapy by the prothrombin and proconvertin test, Owren[154] had only one recurrence *in 13 patients* maintained for 295 patient months at 10 to 30 per cent level. Smith and Schelling point out that these apparently low levels actually correspond, however, to 39–44 per cent and 57–58 per cent in terms of the Quick test (FIG 22). This indicates then the efficacy of only a *moderate* reduction of prothrombin activity. Cosgriff *maintained* in general a *range* between 15 and 30 per cent of normal prothrombin activity. Wood and Conn[8] maintained prothrombin activity at 20 to 35 per cent *of normal*.

My experience and that of my associates *in treating* 304 private patients with chronic cardiovascular disease for periods *ranging from* three months to nine years has led to the conclusion that *in ambulatory* patient a reduction in prothrombin activity to 50 per cent *is satisfactory*.

TREATMENT FOLLOWING ACUTE EMBOLIC OCCLUSION

The detailed treatment of acute embolic arterial occlusion of the extremities is beyond the scope of this monograph and is well discussed in several recent textbooks. Frequently not even the best treatment can avert occasional loss of life and limb. The contribution of surgery to relief of embolism is limited to *indications* of relatively infrequent occurrence. For aortic saddle embolism, as an example, surgery has

of the diseases for which Dicumarol is indicated The wise dictum of Olwin and Friedman[181] should always be considered in treatment 'A little bleeding may be of slight consequence, but a little clotting may mean the difference between a living and a dead patient The only risk that deserves detailed consideration is serious bleeding

Bleeding is serious only when it occurs at a site where immediate vital or irreparable damage is done by a small hemorrhage (as in the brain) or at an inaccessible site where a massive loss can cause death before it can be halted by administration of vitamin K_1, or replaced by transfusion Fatal bleeding has nearly always been from a cerebral artery during treatment for atherosclerosis not for rheumatic heart disease *Among 1334 cases of cardiovascular disease treated by* Beaumont and Tarrit[19] with either Tromexan or phenylindanedione five deaths occurred, all among atherosclerotic patients and all due to cerebral hemorrhage Three of the patients were being treated for cerebral thrombosis and two for hypertensive cardiovascular disease Of the six patients with cerebral hemorrhage (one was not fatal) two had at least 30 per cent of normal prothrombin activity and one had 10 per cent In contrast to this incidence of serious bleeding there were no deaths among 450 patients treated by the same authors for valvular heart disease

Luckey[1 8] believes that nearly all cerebral hemorrhage resulting from treatment can be avoided if the drug is not given in two conditions during the presence of a blood pressure above 160/90 and during the presence of xanthochromia or red cells in the spinal fluid He comments ruefully however that a very small proportion of our patient with cerebral vascular accidents have neither hypertension or xanthochromia

The comparative freedom from serious bleeding among patients with rheumatic heart disease is *borne* out in *other studies probably because* the danger of cerebral hemorrhage is less serious at the earlier age of many patients with rheumatic heart disease than at the older age at which atherosclerotic heart disease develops

Protective Level in Chronic Cardiovascular Disease

In chronic cardiovascular disease since any reduction of prothrombin activity tends to inhibit thrombosis to some extent even a moderate reduction gives adequate protection to many persons Wright Marple and Beck[6] have established this principle in the treatment of myo

200 mg Another 200 mg is given the second day, and 100 mg daily thereafter until the prothrombin content has dropped to 30 per cent The dosage necessary to maintain prothrombin activity at 15 to 30 per cent is then determined After four weeks the daily dose is reduced by 12 5 mg (one half tablet) to permit an increase in prothrombin activity to 50 per cent Usually by the second week the individual reaction to the drug is known and prothrombin activity need be measured only every other day by the third week twice weekly by the fourth week weekly and thereafter at increasing intervals to a maximum of one month The monthly interval between tests is feasible of course because of the greater safety from bleeding assured by maintaining prothrombin at the relatively safe level of 40 to 50 per cent

TESTS OF PROTHROMBIN ACTIVITY

The value of any test of prothrombin activity is to reflect the relation to thrombosis and hemorrhage In the opinion of the majority of hematologists and clinicians at the International Conference at Basel in 1954 *there is no test superior to the one stage Quick test for this purpose It now has the further advantage of widespread use and a wide spread correlation of its values with clinical results* Brambel and Wise[34] observe Since this method measures changes in clotting rate as affected by nonprothrombin entities (activators) and hence give *an over all* picture of the clotting potentialities of blood it is a useful *and practical* tool for this specific purpose *The anticoagulant effect is a complex one which even today is not completely understood* There may be practical advantages in certain instance however in the method of Owren[1] which measures *prothrombin* and proconvertin and its modification by Ware and Stragnell[8] *These methods give accurate results* as late as four days after blood is drawn whereas the Quick test must be done within a few *hours* Owren s suggested range of 10 to 30 per cent corresponds *to* 39 to 57 per cent in the Quick scale (FIG 22)

CHOICE OF ANTITHROMBOTIC DRUG

The choice of a prothrombopenic drug reminds one of a choice among the digitalis *glycosides* which likewise have a qualitatively *similar* action and of which the most effective the clinician finds are those with which he is most familiar Similarly the coumarin and phenyl indanedione derivatives are qualitatively alike in the effect on the

an advantage over expectant treatment and is therefore the advisabl procedure, but such embolism in rheumatic heart disease account fo only about five per cent of clinical occlusion Embolism to the iliac o femoral arteries occurs in about 13 per cent and for these sites al surgery usually is indicated Against these lesser chances looms th 50 per cent incidence of cerebral embolism, with the graver sequela of death and disability, and with no hope as yet of effective operatio Whatever improvement may be promised by developments in surgic technic, embolectomy will remain essentially a palliative rather tha preventive operation The tragedy lies in the probability that seriou occlusion often could have been prevented if earlier minor emboli had been recognized and this applies with special force to cerebr embolism The important treatment in an acute episode therefore directed not at the fait accompli—the embolism—but at preventin further formation and mobilization of the causative thrombi

TREATMENT FOR SURVIVORS OF EMBOLISM

After recovery of the patient from embolism prothrombin activi may be allowed to increase to between 40 and 50 per cent and aft a period of stabilization prothrombin activity need not be determine more often than once a month for most rheumatic patients For som patients even a longer period eventually is considered safe a it i l other investigators Coogan Davis and Petersen [48] find an interval o six weeks satisfactory with some stable patients and Burt [40] speal of one to two months In patients with arteriosclerotic heart disease whom the dangers of hemorrhage are greater a period longer tha three weeks is inadvisable

For four weeks following clinical embolism the prothrombin level maintained at 15 to 30 per cent because of the higher thrombot tendency in the acute condition This is the period of greatest peril o recurrence in rheumatic heart disease and if adequate antithrombot protection is withdrawn for even a day the chance of further emboli is high (FIG 5) If heparin is being administered during the acu stage, Dicumarol can be added—anticipating its maximum effect about 48 hours The daily prothrombin time should be determined o a blood sample obtained just prior to the administration of hepari If the prothrombin content is 100 per cent of normal at the out o 300 mg of Dicumarol is given on the first day if less than 100 per cen

priority The criteria for selection of patients have been discussed previou ly (2) *What is the individual danger of bleeding?* Are foci of bleeding pre ent or uspected? Although mo t bleeding in Dicumarol therapy comes from previou ly latent lesions an increa ed danger may be su pected from the patient s hi tory If there are a ociated hyper tension and arteriosclero i the ri k of cerebral hemorrhage u ually contraindicates the use of Dicumarol Known gastrointestinal le ion or previous bleeding may warn of ma sive hemorrhage (one of the mo t serious but not fatal hemorrhages *in my experience occurred in* a patient with an old apparently quiescent diverticulitis) In myo cardial infarction according to Bay[17] et al Dicumarol therapy is permi sible if there has been a hi tory of duodenal ulcer but no recent establi hed bleeding This policy particularly applies *only to short term* therapy for prolonged treatment a more careful evaluation i neces ary Since liver di ease in itself reduces prothrombin activity it requires pecial caution in treatment but it is not an absolute contraindication Renal impairment is undesirable and any renal *lesion must* be epa rately evaluated as a potential focus for bleeding but it hould al o be remembered that renal impairment may be due to repeated renal embolic infarction *Although impairment* of renal function may not be a con traindication for hort term therapy it increases the ri k *in long term* treatment

Even though the patient s physical condition will permit Dicumarol therapy his per onality or the circumstances of his life may forbid the undertaking of a long range program that demands his close coop eration He mu t be carefully educated in his responsibilities and obvi ou ly he must be re ponsive to such education Only after everal dis quieting early experiences due to our failure in this re pect did my colleagues and I evolve a program which we con ider safe Probably imilar di turbing experiences have discouraged other physicians from further use of the drug

We give each patient printed as well as oral in tructions regarding the early manifestations of abnormal bleeding but ome have not been intelligent enough to follow these in tructions For example one of our early patient who e intelligence was overe timated failed to observe tarry feces recurring for several day Another patient moved away failed to appear for te ts could not be located was kept supplied with Dicumarol by an unknown druggist developed gross hematuria after six months and then came to the office The prothrombin activity was

prothrombin activity the chief difference being in speed and duration of action The phenylindanedione derivatives have the disadvantage however, of sometimes causing agranulocytosis urticaria, and dermatitis Barker [1] reports after having used Tromexan, phenylindanedione and cyclocumarol, we came back again to Dicumarol" Foley [6] suggests,

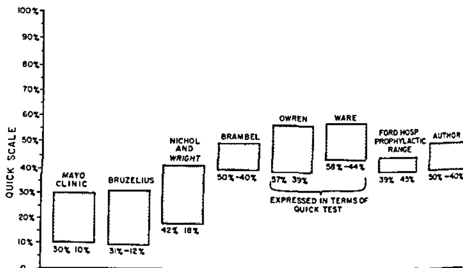


Fig 22 Comparison of degrees of anticoagulation therapeutic range of various authors (By permission from Smith F J and Schelling V The clinical comparison of laboratory methods used in controlling oral anticoagulant therapy in *Thrombosis and Embolism* Proc I International Conference Basel Benno Schwabe & Co 1954)

as quite a series of Dicumarol (dicoumarin) derivative are available and all have been used successfully the choice will be determined primarily by the price In this also the choice resembles that of a digitalis preparation My associates and I have had similar experience to Barker s—Tromexan and phenylindanedione have been found preferable in a few instances but after trying these and other agent we have reverted to Dicumarol using it in prolonged therapy for more than 300 patients with thromboembolic conditions

SELECTION AND EDUCATION OF PATIENT

Before a patient can be considered eligible for continuous treatment several questions must be answered (1) *Is the patient with mitral stenosis eligible for valvoplasty?* If so this treatment should have

a time to tell me I then explained to him why I did not tell him While I am not entirely clear in my memory I think he tated he would have hesitated to remove the tooth if he had known I was taking an anticoagulant Within half an hour after the extraction I think all bleeding had stopped and a clot had formed Ten other patients have had dental extractions while taking Dicumarol without difficulty from bleeding [2]

Another patient ga hed his leg while fishing in Northern California and consulted a local doctor The leg was bleeding only moderately and required only a pres ure bandage When asked later if he had told the doctor he was taking Dicumarol he aid No I thought it might frighten him These instances although eloquent of the degree to whi h fear of bleeding can be conquered emphasize on the other hand another danger—that of overconfidence on the part of the patient, and a failure on our part in proper education Another warning to the patient, therefore must not be overlooked *Never omit reporting the use of Dicumarol to a physician or dentist and always consult the personal physician* In addition the po sibility of an accident with loss of consciousness must be considered A physician patient carries a card which says I am taking Dicumarol as a *medicine In ca e of* injury of even minor degree get *medical* attention Immediately control bleeding by firm pres ure at the site of bleeding We are now giving imilar card to our other patients

Unu ual circum tances at times may lead to the u e of Dicumarol when a trong possibility of severe bleeding may be preferable to the trong pos ibility of serious clotting Bay *et al* [17] *mention* a patient who even preferred the ri k of another massive gastrointestinal *hemor rhage* from a peptic ulcer (he had had three) to the ri k of another myocardial infarction (he had had two) and insisted on being given Dicumarol Mo t patients show *little* concern about occasional bleeding such as purpuric blotches occasional oozing of the gums when the teeth are bru hed or epi taxis so long as they understand it The con cern of a phy ician about *unpredictable* bleeding which a frightened patient or family may interpret as caused by faulty treatment may largely be averted if the possibility of bleeding is properly explained Serious bleeding in a carefully selected patient with the prothrombin level k pt at 50 per cent if *regular reliable* prothrombin determinations are made is rare

less than 10 per cent The bleeding stopped following the administration of vitamin K_1, and the prothrombin concentration quickly rose to normal Since then no patient is accepted for continuous treatment without more critical evaluation

In addition to his intelligence and cooperation the patient must have an understanding of the objectives of treatment must realize the necessity of continuous treatment, and must accept the calculated risk of bleeding If the physician has to bear the complete responsibility for treatment this form of therapy is inadvisable Both the benefits and the dangers are explained frankly and the treatment can then be restricted to those willing to undertake their share in a continuing responsibility Patients are instructed and educated regarding their condition much as a diabetic patient is regarding diabetes The understanding of objectives versus dangers by such carefully screened patients is often quite gratifying They become interested in their prothrombin levels and Dicumarol dosage and accept minor bleeding without alarm The opposite danger to undue fear however occasionally arises the danger of the patient s overconfidence One patient an attorney who needed a dental extraction badly was loath to discontinue the Dicumarol because he had two mild cerebral thromboses when he stopped it previously His statement I would rather bleed than clot Doctor is illustrative of his degree of understanding His oral surgeon was also justifiably loath to extract the tooth unless Dicumarol was discontinued Because of previous experiences with dental extraction without difficulty, we convinced him it was safe The attorney wrote him a letter accepting the risk The dental extraction was accomplished without abnormal bleeding The following year it was necessary to extract another tooth I consented assuming the same oral surgeon would be used He had retired however and the attorney now firmly convinced that the fear of the physician often transcends that of the patient wrote me ' when the time came to have my upper right molar removed and I found that Dr —— had retired from practice I did not tell the extractor for fear that I would have the same trouble with him that I had had with Dr —— A few minutes after the extraction I asked him if he was going to pack it He said no that he did not believe in packing a tooth socket—a natural clot was best I then told him that there might be difficulty in a natural clot formation as I was then taking Dicumarol and my prothrombin level was between 25 and 30 per cent I remember very distinctly that he replied This is a hell of

DISCONTINUANCE OF DICUMAROL

The chief weakness in continuous antithrombotic drug therapy has been the danger of interrupting it for any reason including operation. Such withdrawal of the drug not only restores the original risk of embolism but—according to the experience of many physicians—temporarily increases the risk. Of 17 patients observed by Cosgriff[5] embolism recurred in 12 after Dicumarol was withdrawn—in eight of these within a month. Wright[71] reported serious thromboembolism in 10 of 12 patients with rheumatic heart disease who were not continuously treated and five of these died after withdrawal of the drug. Discontinuance prior to both minor and major surgery has been considered mandatory, although in certain instances serious embolism has occurred. One patient reported by Wright[71] had two systemic arterial emboli when Dicumarol was discontinued before a dental extraction. Facquet, Husson and Ducrot[70] reported a death from cerebral embolism occurring when Dicumarol was discontinued prior to dental extraction. My own experience with a number of patients undergoing dental extraction indicates that it is unnecessary in most instances to stop the drug.[f] Olwin[180] cites an instance of fatal cerebral embolism six days following withdrawal of Dicumarol in preparation for mitral valvoplasty.

The danger of formation and evacuation of a fresh clot is admittedly greatest at mitral valvoplasty, where the source of the emboli is the very site of operation and where the operative procedure itself may dislodge a clot. A large series studied in this connection is that of Ellis and Harken.[6] The problem is usually presented, they find, when a patient has already had one or more peripheral emboli. In their first 500 patients 79 had had emboli and most *of these 79 were* in auricular fibrillation. Of these 17 (more than one out of five) suffered operative embolism. In the next 300 patients, however, although the proportion of patients with *previous* embolism was *greater* (*there* were 60), only six of them (1 out of 10) had operative embolism.

The risk was far greater in patients in *Group 4* (*20 per cent*) than in Group 3 (5 per cent). Most important, since about half of all surgically induced emboli are fatal, the possibility of embolism adds at least three per cent to the danger of death at operation. "Thus the possibility of operative embolism has been significantly decreased as our experience has increased," these authors comment, but it still

Laboratory Control

One other consideration may be described with a brevity that perhaps does less than justice to its importance laboratory control and the supervision of the patient s regimen In my practice, one secretary keep records on all patients receiving Dicumarol supervises appointment for regular laboratory tests, and telephones every patient who fail to keep *an appointment If the patient seems unlikely to maintain* his cooperation the drug is gradually discontinued Laboratory accuracy is guaranteed by the work of two reliable technicians who have made the tests for many years

The printed instructions given each patient may seem to be unduly alarming at first reading Properly explained they are not They merely alert the patient to complications

Printed Instructions Given Dicumarol Patients

> Because of heart disease or chronic thrombophlebiti you are receiving a drug which normally tends to prevent clot formation (Dicumarol or Tromexan) While the e drugs should be *helpful in the treatment of your di ease there is a po sibility* that they may cau e hemorrhage which can be very erious if not checked Hemorrhage ordinarily can be checked and controlled if it is promptly reported to your doctor Symptoms to be reported are
>
> Bleeding from any area
> Nosebleed oozing gums or ruptured skin ve el
> Coughing of blood
> Vomiting of blood
> Blood in the urine (red black or coffee colored urine)
> Bloody black or tarry tool
>
> While taking the e drugs you should not take alicylates (aspirin Alka Seltzer Empirin etc) or liquid or medicinal iron It is al o advisable while taking these drug not to take any patent or adverti ed medicine without consulting your *physician*

We employ the e precautions about salicylates while determining the maintenance dose of Dicumarol When this is e tabli hed we ee no reason to deprive a patient of a small dose of alicylates a an occasional analgesic The dose needed to induce a significant prothrombin *reduction is* quite large (over six grams a day)

cannot prevent all ventricular clots in myocardial infarction it is wishful thinking to assume it can prevent all left auricular clots in rheumatic heart disease Rensen[109] says We have a suspicion that active anticoagulant therapy before operation makes the thrombus in the left atrium more friable Horn concurs[218] We heartily agree with Rensen that in all probability anticoagulants keep the thrombotic material in a more friable gelatinous state and increase the danger of embolus when surgical manipulation is to be undertaken

Janton[1 5] report Quite a few of our patients have been on Dicumarol over a period of one two or more years In every one there was a clot and the center of the clot was soft and of currant jelly consistency Wright[73] however believes the opposite that mural thrombi in the hearts of patients treated for ten days or more with anticoagulants tend to be more smoothly sealed over with a fibrin coating and to possess fewer friable and irregular fibrillating tail

Since Dicumarol is usually discontinued before operation it is possible that the gelatinous friable clots described by Rensen Horn and Janton were those that formed during the preoperative period when the drug was discontinued As a result of these varying opinions however the advisability of the preoperative use of Dicumarol *is not agreed* upon Rensen says[109] We use no anticoagulants for a larger [sic] period preoperatively Horn[118] states We do not use anticoagulants either before during or after surgery and do not believe they are indicated Wright[3] It appears logical to place patients on anticoagulants for from ten to thirty days in preparation for a commissurotomy despite the present lack of statistical proof of its value

The final proof of the effectiveness and safety *of Dicumarol* given throughout the entire preoperative period *must come* from the surgeons

RESULTS FROM DICUMAROL BEFORE AND DURING OPERATION

An important experience in this field is that of Storm and Hansen[7] With Mullertz[239] these investigators maintained antithrombotic prophylaxis through 54 thoracotomies for lung cancer and other diseases in patient for whom the risk of interrupting prophylaxis seemed too great The loss of blood during operation was determined they report and found to be normal as compared with a group of untreated

remains a little higher in patients who have had previous emboli than in the series as a whole " Belcher and Somerville [0] report a comparable experience Five of their 54 patients with preoperative emboli (9 per cent) had further embolism during valvoplasty or shortly afterward

A typical case in my experience was Case 9 in CHAPTER 8 Dicumarol was discontinued two weeks before operation The pathologist reported that "the inner surface of the appendage is almost completely covered by white, organized thrombus while the small lumen remaining contains fresh purple thrombus " Four days after the operation cerebral embolism occurred

The approximate risk of embolism at operation in patient with previous embolism, therefore is about 10 per cent (5 per cent in Group 3 20 per cent in Group 4), and death results in probably half of such accidents If this hurdle of operation is surmounted " Ellis and Harken [58a] conclude the likelihood of late embolization is not great ' By the very operation—the mitral valve opened the auricular appendage removed—the thrombotic milieu is destroyed, through elimination of stasis Any subsequent embolism therefore is unlikely except from clots already pre ent at operation Inasmuch as operative emboli are invariably red and recently formed it is probable the clots have formed in the short preoperative period during which coagulability has been allowed to return to normal The old organized fibrous clots are not u ually dislodged Most recently formed clot if undisturbed presumably have a 50 per cent chance of becoming attached and not ejected (TABLE 5) but the clots formed just prior to operation may not have even this chance Within a few days an exploring finger de pite all precautions may be the factor that precipitates embolism If the patient should be protected against the formation of fresh preoperative thrombi this requires the use of Dicumarol started at an adequate time before and continued throughout operation

To justify such treatment the drug must be shown to be effective and the danger of hemorrhage less than the danger of operative embolism First it must be established that the use of Dicumarol can effectively reduce the incidence of left auricular thrombi and can also affect the clots already present beneficially and not harmfully There is no apparent disagreement regarding the effect of Dicumarol in opposing the formation of clots but there is a sharp division of opinion regarding the effect on the character of a clot which may form despite Dicumarol or of an old clot which already has formed Since Dicumarol

cannot prevent all ventricular clots in myocardial infarction it is wishful thinking to assume it can prevent all left auricular clots in rheumatic heart disease Rensen[199] says We have a suspicion that active anticoagulant therapy before operation makes the thrombus in the left atrium more friable Horn concurs[118] We heartily agree with Rensen that in all probability anticoagulants keep the thrombotic material in a more friable gelatinous state and increase the danger of embolus when surgical manipulation is to be undertaken

Janton[?] reports Quite a few of our patients have been on Dicumarol over a period of one two or more years In every one there was a clot and the center of the clot was soft and of currant jelly consistency Wright[?] however believes the opposite that mural thrombi in the hearts of patients treated for ten days or more with anticoagulants tend to be more smoothly sealed over with a fibrin coating and to possess fewer friable and irregular fibrillating tails

Since Dicumarol is usually discontinued before operation it is possible that the gelatinous friable clots described by Rensen Horn and Janton were those that formed during the preoperative period when the drug was discontinued As a result of these varying opinions however the advisability of the preoperative use of Dicumarol is *not agreed* upon Rensen says[199] We use no anticoagulants for a large [sic] period preoperatively Horn[118] states We do not use anticoagulants *either before* during or after surgery and do not believe they are indicated Wright[?3] It appears logical to place patients on anticoagulants for from ten to thirty days in preparation for a commissurotomy despite the present lack of statistical proof of its value

The final proof of the effectiveness and safety of Dicumarol given throughout the entire preoperative period must come from the surgeon

RESULTS FROM DICUMAROL BEFORE AND DURING OPERATION

An important experience in this field is that of Storm and Hansen[?] With Mullertz[?] these investigators maintained antithrombotic prophylaxis through 54 thoracotomies for lung cancer and other diseases in patients for whom the risk of interrupting prophylaxis seemed too great The loss *of blood during* operation was determined they report and found to be normal as compared with a group of untreated

patients" They later maintained Dicumarol therapy through mitral valvoplasty in 26 cases, finding hemorrhages no greater than in 26 control operations studied at the same time, or in 50 similar operations performed in previous years Of the 26 patients protected by Dicumarol none had thromboembolic complications in the three or four weeks following operation although seven had had thromboembolism However a fresh auricular thrombus was found at operation in one patient who had received Dicumarol for only six days before operation Either the clot had formed before the drug was started or Dicumarol was ineffective In the 26 control patient four had operative cerebral embolism which was fatal in one case and caused residual paralysis in another a fifth patient had a probable cerebral embolism

Antithrombotic Preparation for Operation

Several preoperative procedures using antithrombotic drugs have been advocated in an attempt to prevent operative embolism

1 Dicumarol may be administered before valvoplasty to all patients but discontinued before operation This is based on the belief that Dicumarol not only inhibits formation of new clots but also renders previously formed clots less friable and less likely to be ejected This is inferred from the evidence of Burchell[38] that mural clots formed during Dicumarol therapy in myocardial infarction are less readily ejected from the work of H P Wright[illegible] showing that venous and arterial clots in rabbits are more rapidly canalized with Dicumarol therapy than in its absence and from the observations of I Wright As already discussed others disagree that clots are rendered less friable This procedure may prevent the early formation of clots but does not protect against them the last few days before operation if the drug is discontinued

2 *Dicumarol may be withdrawn before operation in those who are receiving the drug for embolism* but the antithrombotic effect may be maintained up to the time of operation by substituting heparin intravenously for Dicumarol This is the decontrol method advocated by Olwin[180] Heparin and a coumarin or phenylindanedione derivative are given after operation This controls a patient to the moment of operation and respects the surgeon s fear of increased hemorrhage during the operation with a lowered prothrombin activity Likoff[1 5] also believes in continuing Dicumarol until immediately before operation, perhaps

right up to the point of operation the patient's blood coagulability can be controlled with quick acting drugs such as heparin

3 Dicumarol may be given to every patient as a preoperative measure and continued through the operation and for several weeks after as advocated by Storm et al [3]

4 More selectively Dicumarol may be given before during and after cardiotomy only to those patients in whom the risk of operative embolism is considered high—those patients who have had previously diagnosed embolic episodes—since supposedly they face a risk of a 20 per cent incidence of embolism (if in Group 4) and a 5 per cent incidence (if in Group 3) Whether all patients who undergo valvoplasty should receive Dicumarol as suggested by Storm et al must be determined by further experience In patients with previous embolism however the high incidence of operative embolism would seem to justify the continuance of the drug before during and for a short time after operation If antithrombotic drugs have been applied long enough before operation few fresh and potentially embolic clots should be present The final possibility that clots might develop at the suture line after operation can be eliminated by maintaining antithrombotic drug *therapy for* a week or two until this danger is past Although the prothrombin activity is often abruptly elevated by the use of blood transfusions *during* operation the operation itself removes the most important factor in thrombosis—stasis

What of the converse danger—that hemorrhage might occur postoperatively in a surgical wound? In the experience of Storm Hansen and Mullertz [37, 38] this does not occur it might be argued in fact, that any potential site of hemorrhage would be readily evident at operation and could be repaired immediately

Bleeding into the pericardial cavity when the drug is first started following operation has *occurred To begin Dicumarol* soon after operation is probably not advisable since a surgical incision that might not bleed at a 100 per cent level of prothrombin during the operation might and of course did (in those instances of postoperative bleeding) when the prothrombin activity was lowered after operation

SUMMARY

1 *Continuous* antithrombotic drug (Dicumarol) treatment is indicated for patients with mitral stenosis and systemic arterial embolism who are ineligible for mitral valvoplasty and eligible for the drug

2 *Continuous treatment also is indicated (if facilities are adequate)* for patients who survive a severe or recurrent myocardial infarction or even for those who develop the anginal syndrome not responding to other treatment

3 Continuous Dicumarol treatment is safe for the ambulatory patient if the physician is competent, the patient carefully selected, and the laboratory reliable

4 Maintenance of Dicumarol before and during mitral valvoplasty is apparently justified for patients who have had a previous arterial embolism

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